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THE USE OF FAT IN DIABETES MELLITUS AND THE CARBOHYDRATE-FAT RATIO. By WILLIAM SARGENT LADD, M.D., and WALTER W. PALMER, M.D. . . 157
A SIMPLE CLASSIFICATION OF LYMPH-GLAND ENLARGEMENTS, BASED UPON GLANDS REMOVED FOR DIAGNOSIS. By HERBERT FOX, M.D., and DAVID L. FARLEY, M.D. 170
A CONTRIBUTION TO THE PHYSIOLOGY OF THE PINEAL BODY. By YOSITAME IZAWA, M.D. 185
THE RELATION OF ADDISON'S DISEASE TO AMYLOIDOSIS. By MORTON McCUTCHEON, M.D. 197
LYMPHATIC OBSTRUCTION: NON-PARASITIC ELEPHANTIASIS. By L. T. GAGER, M.D. 200
AN ANATOMICAL BASIS FOR FUNCTIONAL MURMURS. By J. EPSTEIN, M.D. . . 208
PAROXYSMAL VENTRICULAR TACHYCARDIA: REPORT OF A CASE OF UNUSUAL TYPE. By DAVID FELBERBAUM, M.D. 211
COSTODIAGHRAGMATIC ADHESIONS AND THEIR INFLUENCE ON THE RESPIRATORY FUNCTION. By WILLIAM S. MIDDLETON, M.D. 222
THE DIAGNOSIS OF TUBAL PREGNANCY. By EMIL NOVAK, M.D. 228
THE ALKALI RESERVE OF THE CEREBROSPINAL FLUID IN VARIOUS STATES OF THE CENTRAL NERVOUS SYSTEM. By RAPHAEL ISAACS, M.A., M.D. . . . 237
BUFFER SOLUTIONS IN INTESTINAL DISEASES. By JOSEPH S. HEPBURN, PH.D., and H. M. EBERHARD, M.D. 244
CREATININEMIA: BASED UPON A STUDY OF FIFTEEN HUNDRED BLOOD CHEMICAL ANALYSES. By HENRY M. FEINBLATT, M.D. 249
OBSERVATIONS ON THE ACTION OF GERMANIUM DIOXIDE IN PERNICIOUS ANEMIA. By M. E. ALEXANDER, M.D. 256
THE ANTISEPTIC AND BACTERICIDAL PROPERTIES OF ISOPROPYL ALCOHOL. By DUDLEY H. GRANT, M.S. 261
STUDIES ON THE REACTIONS OF ASTHMATICS AND ON PASSIVE TRANSFERENCE OF HYPERSUSCEPTIBILITY. By ARENT DE BESCHE, M.D. 265
DIFFERENTIAL DIAGNOSIS OF DIABETES. By HENRY J. JOHN, M.D. 275
INDEX TO ADVERTISERS . . . . . ADV. PAGE 35

Contents continued on page x

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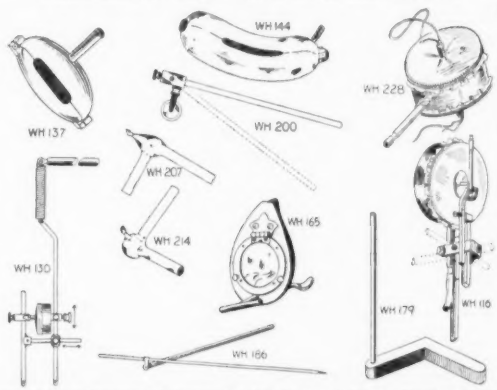

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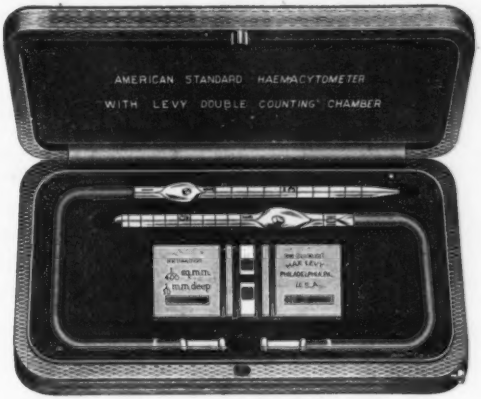

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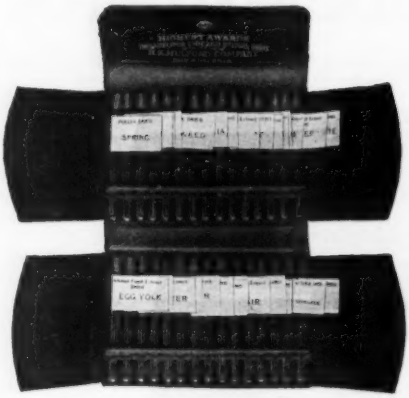

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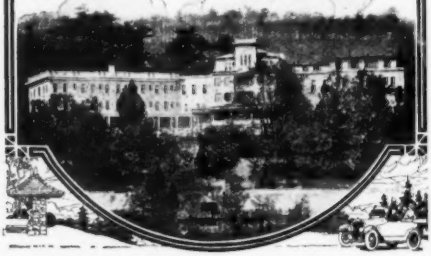

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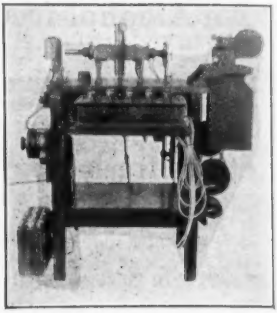

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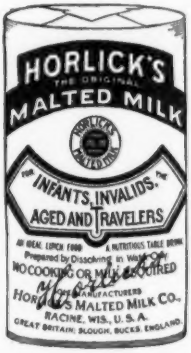

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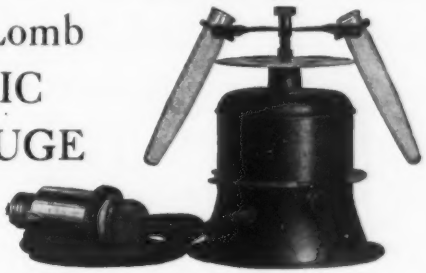

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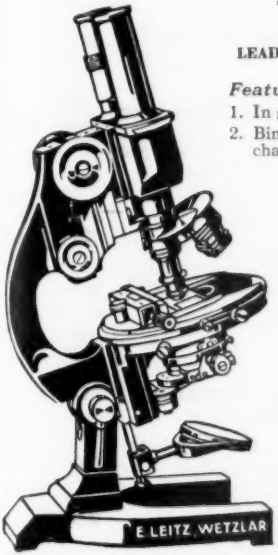

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CONTENTS

ORIGINAL ARTICLES

The Use of Fat in Diabetes Mellitus and the Carbohydrate-fat Ratio . 157
By William Sargent Ladd, M.D., and Walter W. Palmer, M.D., New York.

A Simple Classification of Lymph-gland Enlargements, Based upon Glands Removed for Diagnosis 170
By Herbert Fox, M.D., and David L. Farley, M.D., Philadelphia.

A Contribution to the Physiology of the Pineal Body 185
By Yositame Izawa, M.D., Okayama, Japan.

The Relation of Addison's Disease to Amyloidosis 197
By Morton McCutcheon, M.D., Philadelphia.

Lymphatic Obstruction: Non-parasitic Elephantiasis 200
By L. T. Gager, M.D., New York.

An Anatomical Basis for Functional Murmurs 208
By J. Epstein, M.D., New York.

Paroxysmal Ventricular Tachycardia: Report of a Case of Unusual Type 211
By David Felberbaum, M.D., New York.

Costodiaphragmatic Adhesions and their Influence on the Respiratory Function 222
By William S. Middleton, M.D., Madison, Wis.

The Diagnosis of Tubal Pregnancy 228
By Emil Novak, M.D., Baltimore.

The Alkali Reserve of the Cerebrospinal Fluid in Various States of the Central Nervous System 237
By Raphael Isaacs, M.A., M.D., Cincinnati, Ohio.

Buffer Solutions in Intestinal Diseases 244
By Joseph S. Hepburn, Ph.D., and H. M. Eberhard, M.D., Philadelphia.

Creatininemia: Based upon a Study of Fifteen Hundred Blood Chemical Analyses 249
By Henry M. Feinblatt, M.D., Brooklyn, N. Y.

Observations on the Action of Germanium Dioxide in Pernicious Anemia 256
By M. E. Alexander, M.D., Waterbury, Conn.

The Antiseptic and Bactericidal Properties of Isopropyl Alcohol . . . 261
By Dudley H. Grant, M.S., Elizabeth, N. J.

Studies on the Reactions of Asthmatics and on Passive Transference of Hypersusceptibility 265
By Arent de Besche, M.D., Christiania, Norway.

Differential Diagnosis of Diabetes 275
By Henry J. John, M.D., Cleveland, Ohio.

(Contents continued on page 12)

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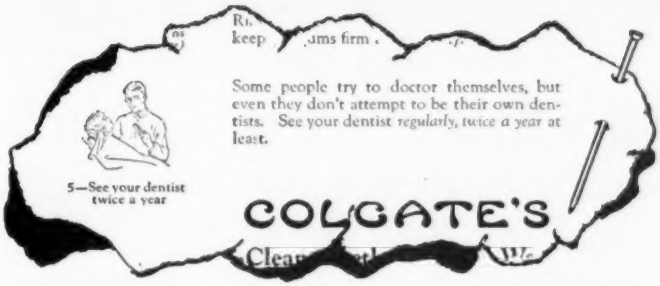
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CONTENTS—(*Continued*)

REVIEWS

Episcopal Hospital Reports. Volume V 281
The Colloidal State in its Medical and Physiological Aspects. By Sir William M. Bayliss, F.R.S., M.A., D.Sc., LL.D. 281
Ueber die pathologische Anatomie der Spirochætosis Ictero—Hæmorrhagica Inada (Weilsche Krankheit). By Prof. Dr. Renjiro Kaneko. 282
The Practice of Medicine in the Tropics. Volume III. By Many Authorities. Edited by W. Byam, O.B.E., Lieut.-Colonel, R.A.M.C. (retired), and R. B. Archibald, D.S.O., M.D., Edinburgh, Major, R.A.M.C. (retired) 282
The Bacteriophage—Its Role in Immunity. By F. D'Herelle, Pasteur Institute. Translation by George H. Smith, Asst. Prof. of Bacteriology, Yale University 283
Environment and Resistance in Tuberculosis. By Allen K. Krause, A.M., M.D. 283
Massage and Medical Gymnastics. By Dr. Emil A. G. Kleen . . . 284
Food and the Principles of Dietetics. By Robert Hutchinson, M.D., Edin., F.R.C.P. 284
Cancer and its Non-surgical Treatment. By L. Duncan Bulkley, A.M., M.D. 285
Abdominal Pain. By Prof. Dr. Norbert Ortner, Translation by William A. Brams, M.D., and Dr. Alfred P. Luger 285
The Spectroscope and its Uses in General Analytical Chemistry. By T. Thorne Baker, A.M.I.E.E., F.R.P.S. 286
Contribution a l'Étude des Manifestations Tardives de l'Encéphalite Épidémique. By Gabrielle Lévy (Service du Professeur Pierre Marie). 287
The Successful Physician. By Verlin C. Thomas, M.D. 287
Orthopedic Surgery. By Sir Robert Jones, K.B.E., C.B. and Robert W. Lovett, M.D., F.A.C.S. 288
Arab Medicine and Surgery; A Study of the Healing Art in Algeria. By M. W. Hilton-Simpson, B.Sc. 288

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W. S. THAYER, M.D., AND ROGER S. MORRIS, M.D.

Further Observations on the Roentgen-ray Treatment of Toxic Goiter . 289
Vaccination of Monkeys against Pneumococcus Type I Pneumonia by Means of Intratracheal Injections of Pneumococcus Type I Vaccine. 291
Observations on the Role of Cockroaches in Disease 291

(*Contents continued on page 14*)

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CONTENTS—(*Continued*)

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.

Ptosis of Right Colon 292
Spondylolisthesis 292
The Metastasizing Tendency of Esophagus Carcinoma 292
Primary Carcinoma of Liver 293
Stoffel Operation for Spastic Paralysis 293
Renal Function Following Nephrotomy 293
The Conservation of Muscles in Paralytic Deformities of the Foot . . 293
The Mercury Inhalation Therapy of Syphilis 294
Coxa Plana and its Causation 294
Tendon Transplantations for Musculospiral Paralysis 294

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D., AND CHARLES C. LIEB, M.D.

Ionic Medication 295
Rheumatoid Arthritis Treated with Intravenous Bacillus Coli Vaccine 295
Observations on the Cause and Cure of Chronic Rheumatism 296
The Scientific Basis for Non-specific Protein Therapy 296

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.

Nasal Diphtheria 297
Osteomyelitis of the Ilium in Children 298
Dietary Consideration in Infantile Eczema 298
A Statistical Study of the Tuberculin Test in Infancy and Early Childhood 299
Brain Tumors in Young Children 300
The Characteristics of the Cerebrospinal Fluid in Postdiphtheritic Paralysis 300
Transfusion through the Umbilical Vein in Hemorrhage of the Newborn:
Report of a Case 301

(*Contents continued on page 16*)

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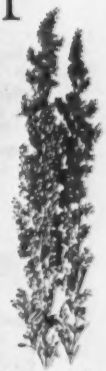

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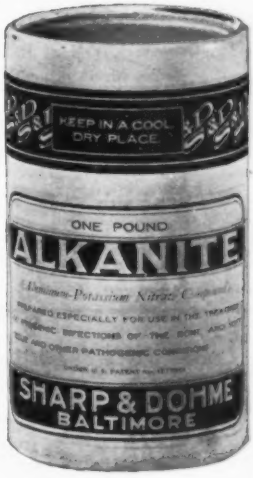

CONTENTS—(*Continued*)

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.

Sodium Thiosulphate 302
The Course of Syphilitic Infection in Pregnant Women 302
Prophylactic Treatment of Syphilis 303
The Treatment of General Paresis by Induced Infection with Malaria Plasmodia 303
Lacquer Dermatitis 304
The Resistance of Hair to Certain Supposed Growth Stimulants . . . 304

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.

Cesarean Section for Double Uterus 305
Use of Pituitrin in the Third Stage of Labor 305
The Anesthetization of Patients for the Classical Cesarean Section . . 306
Is Interference Justifiable in Prolonged Labor? 306
Is the Usual Method of Preparing Patients for Delivery Beneficial or Necessary? 307
Rigidity and Stenosis of the Cervix Complicating Labor 307

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D., AND FRANK B. BLOCK, M.D.

Treatment of Uterine Cancer 307

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D., AND GEORGE W. McCOY, M.D.

Rocky Mountain Spotted Fever: Infectivity of Fasting and Recently Fed Ticks 310
A Toxin-producing Anaërobe Isolated Principally from Fly Larvæ . . 310
The Effect of Vaccinia upon Leprosy 310
Eight Years of Epidemic Poliomyelitis in Montana 310
The Trachoma Problem in the State of Minnesota 311
A Preliminary Report on the Use of Creosote Oil as a Mosquito Repellent 312
Dried Milk Powder in Infant Feeding 312

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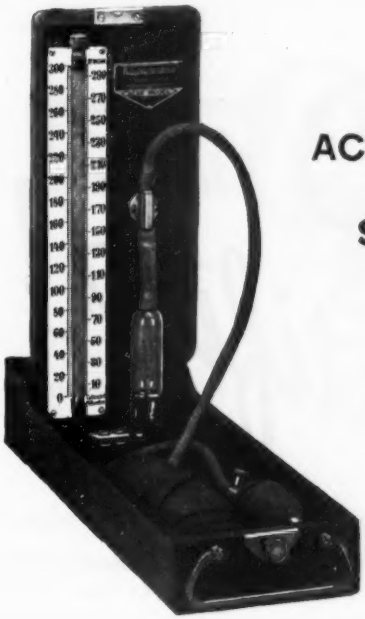

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AUGUST, 1923

ORIGINAL ARTICLES.

THE USE OF FAT IN DIABETES MELLITUS AND THE CARBOHYDRATE–FAT RATIO.*

By William Sargent Ladd, M.D.,

and

Walter W. Palmer, M.D.,

new york.

(From the Chemical Division, Medical Clinic, the Johns Hopkins University and Hospital, and the Department of Medicine of the College of Physicians and Surgeons of Columbia University, and the Presbyterian Hospital, New York.)

Introduction. In diabetes mellitus, the chief disturbance of function is the inability of the body to utilize carbohydrate. Every gram of protein metabolized yields over half its weight in carbohydrate. Therefore, the chief source of energy must be either endogenous or exogenous fat. The complete combustion of fat, however, is limited by the amount of carbohydrate that the body can use, for it is known that glucose must be burned in order to oxidize fat to carbon dioxide and water. Incomplete oxidation of fat results in the production of ketone bodies, and when these substances occur in large amounts, clinical acidosis may result. Until recently, it has been the custom to use relatively small amounts of fat in the diets of diabetics. The relatively high caloric value, the protein sparing action and the relatively low specific dynamic action of fat are advantages in favor of its use, which frequently make it desirable to feed it in the largest amounts possible without producing any significant ketosis. This may be done without danger if we know the amount of fat that is com-

* The work reported in this paper was presented in abstract before the Society for Experimental Biology and Medicine, Proceedings, 1920, **18**, 109, and Association of American Physicians, Transactions, 1921, **36**, 266.

pletely oxidized through the oxidation of a given amount of carbohydrate. In view of the importance of this question, we have undertaken the problem of determining whether anything like a fixed ratio for this relationship exists; whether such a ratio is alike in normal and diabetic persons, and whether it is the same for all cases of diabetes, and if so, of determining its limits so that it may be applied in dietary treatment.

Literature. This subject has received much attention for many years, and its importance is quite generally appreciated. The chemical mechanism involved in the probable reactionary substances, acetone bodies or precursors, and glucose has been discussed by Geelmuyden,[1] Woodyatt,[2] Ringer[3] and Shaffer.[4] Only recently has any work of a quantitative nature appeared leading to practical appreciation in the dietary treatment of diabetes. Zeller,[5] in his studies upon the influence of fat and carbohydrate upon protein starvation, observed that when the nitrogen intake was reduced to a very low level, and the fat and carbohydrate ingestion so adjusted that the carbohydrate fraction of a diet, adequate in caloric value, amounted to 10 per cent of the total calories—approximately 1 gm. of carbohydrate to 4 gm. of fat—there was a marked increase in the amount of ketone bodies in the urine. When the carbohydrate intake was reduced still lower, to 5 per cent, there was a large amount of ketone bodies present in the urine, associated with headache and general malaise. Lusk[6] made the suggestive comment on Zeller's experiment that "In the normal combustion of fat, each molecule of β-oxybutyric acid, which is the end-product of the oxidation of each fatty acid, requires the presence of a triose molecule." The work of Lang[7] may be cited as suggestive of a definite carbohydrate-fat ratio for the complete oxidation of the fatty acid radical of the latter, although the experiments are not devised to establish a very close quantitative relationship. The subject has received a new impetus through the interesting work and discussion of Shaffer.[4] Furthermore, Newburgh and Marsh[8] have reported success in the treatment of diabetes with diet high in fat. Evidence is brought forward by Shaffer[4] that *in vitro* acetoacetic acid rapidly disappears in the presence of glucose and hydrogen peroxide in an alkaline solution. Turning his attention to the process involved in the organism, he presents interesting calculations of the ketogenic and antiketogenic factors metabolized, first suggesting that 1 molecule of glucose (antiketogenic) must be formed to oxidize completely 1 molecule of fatty acid (ketogenic), and later 1 of glucose to 2 of fatty acid. Following Shaffer, Woodyatt,[9] Hubbard and Wright,[10] Wilder, Boothby and Beeler,[11] and others have presented evidence together with a discussion of certain theoretical considerations bearing on a definite carbohydrate-fat ratio. Our studies were begun in the autumn of 1919, as a result of its importance in the dietary treatment of diabetes, and the sugges-

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tive work of Zeller, with Lusk's comments, and without the knowledge of the work then in progress in Shaffer's laboratory.

Experimental. The endeavor was made to eliminate in the experimental procedure as many variables as possible in order to simplify the interpretation of results. In our subjects, the following conditions were successfully established in most instances.

1. The patients selected presented uncomplicated diabetes mellitus.

2. For several days previous to, and at the beginning of the experiment, the urine gave no reaction for acetone and acetoacetic acid by sodium-nitroprusside test, and the daily excretion of the ketone bodies estimated quantitatively was within normal limits.

3. The diet was so adjusted that the urine did not reduce Benedict's solution.

4. Nitrogen equilibrium was maintained throughout the experiment, thus tending to stabilize, so far as possible, the protein factor in the intermediary metabolism.

5. There was little change in body-weight.

The procedure has been, by dietary measures, to render the urine free from sugar and ketone bodies, and to determine the food tolerance. When this is established, the subject is given a diet, the total calories of which (together with the protein quota) are calculated to establish and maintain nitrogen equilibrium. The carbohydrate and fat are varied isodynamically with at first relatively high carbohydrate, gradually increasing the fat until ketone bodies appeared in the urine, as evidenced by qualitative tests, or showed by quantitative estimation a definite increase over the earlier average excretion. The protein quota of the diet, approximating 10 per cent of the total calories, was kept constant throughout the experiment.

When nitrogen equilibrium and weight are maintained for periods of days or weeks, it seems probable that the daily total metabolism is fairly constant, and furnished by the food taken. We assume that the carbohydrate taken in the food is utilized since the patient remained sugar free. Protein metabolism was estimated from the urine nitrogen. Examination of the stools for macroscopical and microscopical fat, as well as quantitative estimations of the daily amount (3 to 7 per cent) in 2 cases, have convinced us that at least 95 per cent of the ingested fat is absorbed and may be utilized. In this connection, attention may be called to the work of Hill and Bloor,[12] indicating that normally all fat fed is absorbed, and that the fat in the feces represents fat excreted. However, fat excreted is not utilized.

In those cases where nitrogen equilibrium could not be maintained, and where weight loss was present, the fat burned was calculated from the difference between the calories furnished by the protein and carbohydrate, metabolized, and the estimated total

metabolism. Estimates were obtained from basal metabolism studies or the formula of Du Bois.[13] Twenty per cent was added for rest in bed, and 40 per cent for being up and about the ward.

The following chemical methods were employed: For urine nitrogen, the Kjeldahl method for total nitrogen; for acetone bodies, the method of Van Slyke and Fitz;[14] for blood sugar, the method of Folin.[15] All the determinations were made in duplicate and checked.

Basal metabolism determinations were made with Tissot gasometer.

In the main, all diets are calculated from Atwater and Bryant's tables.[16] For certain food values, *Bulletin* 220, Pt. II, Connecticut Agricultural Experimental Station, and data furnished by the Department of Nutrition of Columbia University and the Presbyterian Hospital were consulted. The fat percentage of the cream used was determined directly by analysis. All food was cooked in the dishes in which it was served; all weighings were checked and corrections made for food returned. The value of the caloric estimations of these diets is discussed later in this paper.

TABLE I.

Case No.	Increase in ketone bodies shown by test.	In nitrogen equilibrium, No. wt. loss.	Fat burned estimated.	Ratio for period of increase.	Length of shift periods.
I.	Qual.	Yes	No	2.5	Daily shift.
II.	Quan.	No	Yes	3.8	Daily shift.
III.	Quan.	No	Yes	2.7	Daily shift.
IV.	Qual.	Yes	No	4.1	Daily shift.
V.	Qual.	No	Yes	3.8	Daily shift.
VII. (Normal) .	Qual.	Yes	No	4.2	Daily shift.
IX.	Quan.	No	Yes	4.6	3 to 4 days.
X. (Case III, 2d admission)	Quan.	No	Yes	3.4	2 days.
XI.	Quan.	Yes	No	4.2	3 to 5 days.
XII.	Quan.	Yes	No	4.3	5 days.
XIII.	Quan.	Yes	No	5.8	5 days or longer.
XV.	Quan.	Yes	No	5.8	5 days or longer.

In Table I, we have summarized the cases in order to show the ratios of available carbohydrate to fat at which ketone bodies appeared quantitatively or showed a marked qualitative increase in the urine. The formula adopted for the expression of the ratios is:

$$\frac{F}{G} = \frac{\text{gm. fat}}{0.58 \text{ gm. P} + \text{gm. CH}}$$

(F = fat, G = available carbohydrate, P = protein, CH = carbohydrate.) The average value for the ratio at which ketone bodies appeared in the urine by qualitative test (sodium nitroprusside), or showed a definite increase quantitatively, is 4 gm. of fat to 1 gm. of available carbohydrate. This formula makes

no allowance for possible antiketogenic action of fat nor for the possible ketogenic action of protein as do most of the formulæ which have been recently presented. The formula suggested by Shaffer is based on certain assumptions as to the ketogenic and antiketogenic factors of the food elements. The ketogenic factor for protein is based upon the one analysis of ox muscle by Osborn.[6] The variation in the amino-acid content is uncertain, and the ketogenic value of protein is yet to be demonstrated with the same degree of probability as its glucose yielding (antiketogenic) capacity. The antiketogenic factor for fat is based on the still quite debatable question of whether the glyceride of the fatty acid is metabolized in the same manner as glycerol. Lusk[6] states that "Giving fat with meat to a diabetic will not ordinarily increase the sugar in the urine. The writer has never observed such an increase in any of the work of his laboratory. On giving meat in diabetes, the fat metabolism is reduced as it would be in the normal organism, and yet there is no effect on the D:N ratio, and therefore the latter cannot be influenced by the quantity of fat burned." Although the D:N ratio of 3.65 is not conclusively proven, this figure is generally accepted. Shaffer has discussed in detail the ketogenic and antiketogenic factors of metabolized food in several papers. We have reached the conclusion that the formula, as presented above, is an expression, in terms of grams of available carbohydrate and grams of fat, which can be applied more simply in the every-day calculation of diets than most other formulæ, and with equal safety.

We give in detail a portion of the data from Case XV in Table II. Only the periods which are essential for discussion are presented. The patient, a male, aged twenty-five years (height 168.1 cm.; weight, 54 kilos), served with the army in France. He returned apparently in good health. Late in the summer of 1921, he noticed thirst, rapid loss of weight and weakness, for a period of six weeks. He was admitted to the hospital on October 15. The blood sugar was 1.81 mgm. per 100 cc; blood CO_2, 24.7 vols. per cent. Clinically, he was the picture of acute diabetes. After several days of a reduced diet and starvation, his urine became free from sugar and acetone. The diet was then gradually increased until it proved a maintenance diet. Repeated basal metabolism determinations have shown his rate to be a total of 54 calories per hour, or a variation from normal standard of about −13 per cent. The patient, being an employee of the hospital, returned to his active duties and has coöperated with us with great care and fidelity in all details. His diet has been furnished by the metabolism kitchen of the hospital, the case being carefully followed for over a year. During this period, his weight has been maintained at between 54 and 55 kilos, he has remained sugar free and continued his usual duties. The diet during this period has had an approximate value of basal plus 105 per cent.

TABLE II.

Date.	Carbohydrate.	Protein.	Fat.	Urine N.	Total ketone bodies as acetone, gms.	Weight.	Blood sugar, mg. 100 cc.
	Period II.—$\frac{F}{G} = \frac{F}{0.58\,P + CH} = \frac{212}{109} = 1.95$						
Feb. 22	80	50	212	8.7	0.365		
23	80	50	212	8.3	0.178	...	0.91
27	80	50	212	7.5	0.297		
28	80	50	212	6.7	0.206		
Mar. 1	80	50	212	8.0	0.239	54.4	
2	80	50	212	8.8	0.427		
5	80	50	212	8.2	0.347		
6	80	50	212	8.2	0.347		
7	80	50	212	7.5	0.406	54.6	
8	80	50	212	5.3	0.253		
9	80	50	212	7.1	0.376		
				average 7.7			
	Period III.—$\frac{F}{G} = \frac{235}{109} = 2.14$						
Mar. 12	80	50	235				
13	80	50	235	5.5	0.600	54.2	
14	80	50	235	5.6	0.397	...	0.90
15	80	50	235	5.6	0.382		
16	80	50	235	6.5	0.448		
19	80	50	235	4.8	0.535		
20	80	50	235	5.5	0.426	54.2	
				average 5.6			
	Period IV.—$\frac{F}{G} = \frac{247}{82} = 3.0$						
Mar. 21	53	50	247	4.7	0.784		
22	53	50	247	5.0	0.800		
23	53	50	247	6.1	1.805		
	53	50	247	...	...	54.4	
26	53	50	247	4.4	1.580		
27	53	50	6.7	1.480			
28	53	50	247	6.4	1.300	54.4	
29	53	50	247	5.1	2.250	...	0.93
30	53	50	247	6.9	1.280		
	53	50	247	...	...	54.4	
April 2	53	50	247	6.2	1.670		
3	53	50	247	5.8	2.790		
4	53	50	247	5.1	1.740	54.2	
5	53	50	247	6.8	1.410		
6	53	50	247	6.5	1.610		
7	53	50	247	6.7	1.520		
				average			
10	53	50	247	5.3	...	54.3	0.87

TABLE II.—*Continued.*

Date.	Carbohydrate.	Protein.	Fat	Urine N.	Total ketone bodies as acetone, gms.	Weight.	Blood sugar, mg. 100 cc.
PERIOD V.—$\frac{F}{G} = \frac{264}{46} = 5.74$							
April 13	17	50	264	6.3	4.29	54.4	
14	17	50	264	6.9	3.29		
15	17	50	264	5.5	3.70		
16	17	50	264	5.5	3.70	...	0.81
18	17	50	264	7.4	3.16	56.2	
19	17	50	264	5.6	1.91		
20	17	50	264	6.7	2.50		
24	17	50	264	5.5	1.49		
25	17	50	264	6.6	1.80	54.1	
26	17	50	264	6.7	2.78		
27	17	50	264	8.7	2.21		
May 2	17	50	264				
3	17	50	264	7.6	0.10	54.1	
4	17	50	264	6.9	1.86	...	0.92
8	17	50	264	7.0	1.30	54.3	
9	17	50	264	6.5	1.75		
10	17	50	264	5.1	1.47		
11	17	50	264	7.4	1.85		
12	17	50	264	5.9	1.87	54.3	
14	17	50	264	4.6	2.38		
15	17	50	264	8.4	1.47		
16	17	50	264	7.1 average 6.6	1.37	54.4	
PERIOD VI.—$\frac{F}{G} = 3.0$							
May 17	53	50	247	8.2	1.860		
18	53	50	247	6.6	0.670		
21	53	50	247	5.1	0.460	54.5	
22	53	50	247	4.6			
23	53	50	247	5.4			
24	53	50	247	6.1	0.610	...	0.95
25	53	50	247	6.3	0.620	54.4	
26	53	50	247				
27	53	50	247				
30	53	50	247	5.7	0.410		
31	53	50	247	6.4 average 6.0	0.520		
PERIOD VII.—$\frac{F}{G} = 2.14$							
June 4	80	50	235				
5	80	50	235	...	...	54.2	
6	80	50	235				
7	80	50	235	...	...	...	0.94
8	80	50	235	5.5	0.30		
9	80	50	235	5.5	0.30	54.2	

In considering the estimated values of given diets calculated from Atwater and Bryant's tables, we wish to point out certain facts, and discuss their bearing on the work here presented. We have selected for purposes of illustration the diet given on March 22, in Table II, the only part of the period in which the excretion of ketone bodies increased markedly, and have prepared Table III from Atwater and Bryant's tables, giving minimum, average, and maximum values for the articles of food used this particular day.

TABLE III.

Food.	Grams.	Carbohydrate.			Protein.			Fat.		
		Min.	Ave.	Max.	Min.	Ave.	Max.	Min.	Ave.	Max.
Orange . .	EP 100	11.6	11.6	18.5	0.8	0.8	1.1	0.1	0.2	0.3
Butter . .	80	0.0	0.0	0.0	0.8	0.8	0.8	68.0	68.0	68.0
Cream . .	250	7.5	7.5	7.5	5.5	5.5	5.5	100.0	100.0	100.0
Eggs . . .	EP (2) (100)	0.0	0.0	0.0	10.0	13.4	16.0	8.6	10.5	15.1
Bacon . .	EP 50	0.0	0.0	0.0	3.2	5.0	9.0	20.0	33.7	39.9
Ham . . .	EP 55	0.0	0.0	0.0	6.6	10.9	12.6	9.5	11.4	31.2
Lettuce . .	EP 50	0.8	1.5	2.5	0.4	0.6	0.9	0.1	0.2	0.3
Rutabaga .	EP 100	6.2	8.5	10.3	0.9	1.3	2.0	0.1	0.2	0.3
Green pepper	EP 50	2.3	2.3	2.5	0.8	0.8	0.8	0.1	0.1	0.1
Cauliflower .	AP 50	1.7	2.4	3.0	0.8	0.9	1.0	0.1	0.3	0.4
Tomato . .	AP 50	1.0	2.0	3.3	0.2	0.5	0.7	0.1	0.2	0.7
Sauerkraut .	AP 100	3.3	3.8	4.4	1.5	1.7	1.9	0.2	0.5	0.8
Asparagus	AP 100	2.2	2.8	4.1	0.9	1.5	2.4	0.0	0.1	0.2
Carrots . .	EP 50	3.3	4.7	6.9	0.4	0.6	1.0	0.0	0.2	0.4
Peas . . .	AP 25	1.2	2.5	4.4	0.4	0.9	1.5	0.0	0.1	0.2
Walnuts . .	EP 10	1.3	1.3	1.9	1.4	1.8	2.0	6.0	6.4	6.7
Cream cheese	AP 10	0.1	0.2	0.4	1.8	2.6	3.7	2 5	3.4	4.5
Celery . .	EP 10	0.3	0.3	0.5	0.1	0.1	0.1	0.0	0.0	0.0
Olives . .	EP 10	1.2	1.2	1.2	0.1	0.1	0.1	2.8	2.8	2.8
Oil . . .	8	0.0	0.0	0.0	0.0	0.0	0.0	8.0	8.0	8.0
Total . .		44.1	52.6	71.2	36.6	79.8	63.1	226.1	246.3	279.9

For this day (March 22, Table II), the diet desired was one yielding carbohydrate (53 gm.), protein (50 gm.) and fat (247 gm.), which, on the basis of our calculation, gives a carbohydrate-fat ratio of 1 : 3. The average values yield approximately these amounts. Furthermore, it is observed that, although these amounts furnish the carbohydrate-fat ratio desired for the patient within the limitations of our experiment, any other combination of the minimum, average or maximum values shown gives a very different value for the ratio computed by the same formula.

Thus: Min. Ch = 44.1. Average P = 49.8. Max. fat = 279.9. Substituting

$$\frac{\text{Fat}}{0.58\,\text{P} + \text{CH}} = \frac{279.9}{29 + 44.1} = 3.84$$

Using another combination, we have: Max. CH = 71.2. Average P = 49.8. Min. fat = 226.1. Substituting

$$\frac{\text{Fat}}{0.58\,\text{P} + \text{CH}} = \frac{226.1}{29 + 71.2} = 2.26$$

Ratios computed by other formulæ would likewise vary. Therefore, it is quite apparent that for any given day, the error may be considerably more than is consistent with the purpose of the experiment.

Although we do not know that Case XV was actually burning 2700 calories per day (which in his case = basal + 105 per cent), he was approximately in nitrogen equilibrium for a period of months, with no significant variation in weight. The nitrogen content of the above diets are: Minimum, 5.86 gm.; average, 7.97 gm.; maximum, 10.1 gm. The patient's nitrogen excretion for the day was 6 gm. (5 + 1 gm. for feces nitrogen). During the whole experiment, the nitrogen excretion varied from 4.4 gm. to 8.7 gm., which, with the addition of 1 gm. for feces nitrogen, makes the total excretion 5.4 gm. to 9.7 gm.; whereas the minimum and maximum variation for food nitrogen, as calculated from Atwater and Bryant's tables, is 5.86 to 10.1 gm. The average calculated nitrogen intake is 8 gm. and the average excretion, plus 1 gm. for feces nitrogen, is approximately the same. However, taking into account these discrepancies on the one hand, and the fact that the body weight was maintained constant over so long a period on the other, we feel justified in concluding that the patient was in food equilibrium. No attempt was made to control the water balance. We have appreciated from the outset the necessity of knowing what foodstuffs are actually burned in the body at the time there is an increase in the production of ketone bodies in order to estimate with even approximate accuracy the carbohydrate-fat ratio. The means for securing data of any great significance have not been available, for the only methods at hand were those used in the determination of basal metabolism and respiratory quotients, clinically.

In the earlier cases (Table I), where daily shifts were made, the ratios were more variable than in the later cases. It became apparent, as our work proceeded, that calculations based upon such short periods were not accurate indications of the actual metabolic conditions, partly, at least, because of this possible error in calculated food values. Therefore, whenever possible, we lengthened the periods of each isodynamic shift. We are convinced that this criticism holds for much of the work on the carbohydrate-fat ratio presented elsewhere.

It is interesting to apply the data presented in Period V of Table II to Shaffer's[4] revised formula. The food fed is 17 gm.

of carbohydrate, 50 gm. of protein and 260 gm. of fat. The urine nitrogen averages 6.6 gm. per day (adding 1 gm. for feces nitrogen = 7.6 gm.). The nitrogen intake averages 8 gm.

$$\frac{\text{(Total calories of energy exchange)} - (100 \times \text{urine N})}{50} = \text{grams}$$

food carbohydrate to provide approximate ketogenic balance, or

$$\frac{2730 - 660}{50} = \frac{2070}{50} = 41$$

or 41 gm. of food carbohydrate must be burned to prevent ketosis. Slight ketosis occurred with only 17 gm. of food carbohydrate.

Calculating the expected ketone excretion, using Shaffer's[4] factors, we have:

		Ketogenic millimols.	Antiketogenic millimols.
Glucose,	17.0 gm. × 5.56	..	94.6
Urine N,	6.6 gm. × 15.00	99.1	
	× 20.00	..	132.0
Fat,	264.0 gm. × 3.43	905.5	
	× 0.57	..	150.5
Total millimols		1004.6	377.1

Assuming 1 millimol of antiketogenic substance equivalent to 2 millimols of ketogenic substance, then 1004.6 − (2 × 377.1) = 250.6 excess ketogenic millimols. Expected ketone excretion would be, then, 250.6 × 0.104 = 25.2 gm. ketoacid. However, but 4.29 gm. ketoacid were excreted.

Applied to Woodyatt's formula

$$\frac{FA}{G} = \frac{0.46\,P + 0.9\,F}{0.58\,P + CH + 0.1\,F} = \frac{23 + 238}{29 + 17 + 26} = \frac{261}{72} = 3.57$$

or a ratio which would lead one to expect a marked ketone body excretion.

Likewise, applying Hubbard's calculations,[10] 264 gm. of fat should yield approximately 250 gm. of fatty acid. With the assumed ratio of 1 mol. glucose to 2 mols. fatty acid, the glycerol of fat should help completely oxidize about one-third, or 84 gm., of this fatty acid. The glucose from protein in excess of that used for the amino-acid ketogenic equivalent of protein would help oxidize 0.25 × 50 = 12.5 × 1.5 (reducing to terms of fatty acid molecular equivalents) × 2 = 37.5 gm. of fatty acid. The 17 gm. of food carbohydrate would account for 17 × 1.5 × 2 = 51 gm. of fatty acid, or 84 + 37.5 + 51 = 172.5 gm. of fatty acid. This amount of fatty acid could be accounted for by the antiketogenic factors, leaving a balance of 250 − 172.5 = 77.5 gm. of fatty acid to be excreted.

Discussion. It is apparent, then, that the calculations based upon the assumptions of the authors quoted do not hold for the

case under discussion, nor do they hold for the majority of our cases. This discrepancy between calculated and observed findings is appreciated by these authors.

The point we wish to emphasize is that, although we have no solution for this difficulty in regard to the chemical relationships involved in the ketogenic-antiketogenic ratio, our data tend to show that fat can probably be given to many diabetics in ratios still higher (see Table I) than any yet proposed. And that as yet, the simple gram ratio of available carbohydrate to fat is most satisfactory for practical purposes. One case which has maintained body-weight and preserved a normal blood sugar has been followed for one year on a diet in which the carbohydrate-fat ratio was high.

There have come to light in the study of the subject facts which require special emphasis:

1. We have been able to attain such high ratios only in cases where a relatively high-fat diet has been introduced by gradual increases in the fat, with a correspondingly gradual reduction in the carbohydrate.

2. In severe cases entering the hospital with blood CO_2 of 25 vol. per cent, or less, we have been unable to give a high ratio carbohydrate-fat diet immediately without a fall in the blood CO_2 and grave symptoms of acidosis. Our experience has been the same, whether the total calories of the diet given were low or calculated to maintain the patient's metabolism. This observation has led us to question whether there is a difference between the effect of ingested fat and body fat on ketone production. We are not prepared to make further comment on this point at present, beyond the statement that we have accomplished by starvation or low protein and carbohydrate intake what we could not accomplish by diets of greater caloric value regardless of the amount of fat. In other words, we have been able to clear up sugar and acetone excretion more quickly in the majority of cases, without apparent injury to the patient, by undernutrition to the point of starvation. This subject is to be discussed in a subsequent paper. After the patient has been rendered sugar and acetone free, we have gradually increased the fat to a high ratio, which has been maintained for months without apparent deleterious effect upon the patient, although accompanied by a considerable excretion of ketone bodies.

3. If Periods IV and VI, III and VII, Table II, are compared, it is observed that the acetone excretion in the later periods is less, although apparently the same amounts of foodstuffs are being burned. Often when an isodynamic shift is made, there is an increase in the ketone excretion which tends to subside as the period continues. This suggests that certain adjustments in the complete oxidation of fat take place slowly.

4. When complications, such as an acidosis or infection are present, it has been impossible to feed fat in such relatively large amounts.

Our procedure today is to render sugar and acetone free by starvation or undernutrition on a low-protein and carbohydrate diet as formerly, then to increase the fat to a relatively high ratio (usualy 3 to 4) in relation to the available carbohydrate, and lastly to work out dietary tolerance by increasing all constituents at intervals of two or four days. Observation of fasting (A.M.) blood-sugar values with each increase provides a valuable check upon the advisability of increase. In milder cases, the blood-sugar may be kept normal and a maintenance diet given, while in the more severe cases, the blood-sugar often rises above normal values without glycosuria, but with the continuance of a maintenance diet. We are faced with the fact that in many severe cases, it is often impossible to render sugar or acetone free, and at the same time provide a maintenance diet. However, high-fat diets have been tolerated after being gradually attained with an increase in the strength and subjective well-being of the patient.

Summary. 1. The carbohydrate-fat (antiketogenic-ketogenic) ratio, which leads to an increase in production of ketone bodies, has been determined in 11 cases of diabetes mellitus and 1 normal individual.

2. When the ratio is computed from the carbohydrate in the food plus 58 per cent of the protein in grams and the fat in grams, it is approximately 1:4 in both diabetic and normal subjects. That is,

$$\frac{F}{G} = \frac{\text{gm. fat}}{0.58\ \text{gm. P} + \text{gm. CH}} = \frac{4}{1}$$

3. The difficulties of calculating the antiketogenic-ketogenic ratio upon the more accurate molecular basis suggested by Shaffer is discussed.

4. Briefly, the facts are: (*a*) Lack of data as to what food elements are being burned by the body; (*b*) the part fat may take in antiketogenesis; and (*c*) the role of protein in ketogenesis.

5. The time factor in the adjustment of the body metabolism to changes in the carbohydrate-fat ratio is demonstrated.

6. Attention is called to the error which may occur in the use of tables for calculating food values. We have attempted to minimize the error by observing the effect of the diet over long periods, after making isodynamic shifts in the diet at widely separated intervals. The maintenance of a constant weight and nitrogen equilibrium in these long periods lends support to our opinion that the food taken is approximately the food burned.

7. Relatively large amounts of fat may be used in diabetic

diets without injury to the patient. There are, however, the following qualifications:

(*a*) We have been able to free the urine from sugar and acetone bodies more quickly by undernutrition to the point of starvation than by any diet where exogenous fat is substituted for the amount of body-fat assumed to be burned.

(*b*) There is need, as yet, to follow carefully any severe case of diabetes where the ratio is not well within the limits of 1 to 4.

(*c*) In the presence of infection or an already severe ketonuria, high-fat diets are not advised.

8. Our method of procedure in the dietary treatment of diabetes has been briefly outlined.

Conclusion. 1. The carbohydrate-fat ratio, at which the ketone bodies fail to be completely oxidized is apparently fixed, and is the same for both normal and diabetic individuals.

2. For practical purposes, the carbohydrate-fat ratio of 1 : 4, calculated from the formula

$$\frac{F}{G} = \frac{\text{Fat in grams}}{0.58 \text{ gm. P} + \text{gm. CH}}$$

is the most serviceable in the construction of diets where it is desired to obtain a maximum caloric intake with a minimum in the form of carbohydrate.*

* We submit these findings in spite of the great advances made in the treatment of diabetes by the brilliant work of Dr. Banting and others, because we feel that adequate dietary control will remain the basis of treatment for many cases, especially those of the milder type. Furthermore, if an extract can enable the body to burn a known amount of carbohydrate, a knowledge of the carbohydrate-fat ratio will enable us to use fat in amounts which will insure the greatest energy possible, especially in the severest cases.

BIBLIOGRAPHY.

1. Geelmuyden, D. C.: Ztschr. f. physiol. Chem., 1904, **41**, 135.
2. Woodyatt, R. T.: Jour. Am. Med. Assn., 1910, **55**, 2109; Jour. Biol. Chem., 1915, **20**, 129; Jour. Am. Med. Assn., 1916, **66**, 1910.
3. Ringer, A. I.: Jour. Biol. Chem., 1914, **17**, 107.
4. Shaffer, P. A.: Jour. Biol. Chem., 1921, **47**, 449; 1921, **47**, 433, 1921, **49**, 143; 1922, **54**, 407.
5. Zeller, Heinrich: Arch. f. Physiol., Leipzig, 1914, p. 213.
6. Lusk, G.: Elements and Science of Nutrition, 1917, third edition.
7. Lang, R. M.: Biochem. Jour., 1915, **9**, 456.
8. Newburgh, L. H and Marsh, P. L.: Arch. Int. Med., 1920, **26**, 647; 1921, **27**, 699.
9. Woodyatt, R. T.: Arch. Int. Med., 1921, **28**, 125.
10. Hubbard, R. S., and Wright, F. R.: Jour. Biol. Chem., 1921, **50**, 366.
11. Wilder, R. M., Boothby, W. M., and Beeler, Carol: Jour. Biol. Chem., 1922, **51**, 311.
12. Hill, Elsie, and Bloor, W. R.: Jour. Biol. Chem., 1922, **53**, 1, 171.
13. Du Bois, D., and Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 863. Du Bois, D., and Du Bois, E. F.: Arch. Int. Med., 1915, **15**, 868. Gephart, F. C., and Du Bois, E. F.: Arch. Int. Med., 1916, **17**, 902.
14. Van Slyke, D. D., and Fitz, R.: Jour. Biol. Chem., 1917, **32**, 495.
15. Folin, Otto: Jour. Biol. Chem., 1919, **38**, 259.
16. Bryant, A. P., and Atwater, W. O.: Bulletin No. 28, U. S. Dept. of Agriculture.

A SIMPLE CLASSIFICATION OF LYMPH-GLAND ENLARGEMENTS, BASED UPON GLANDS REMOVED FOR DIAGNOSIS.

By Herbert Fox, M.D.,

AND

David L. Farley, M.D.

PHILADELPHIA.

(From the William Pepper Laboratory of Clinical Medicine, University of Pennsylvania.)

There has been no dearth of attempts at the classification of the lymphadenopathies, during the history of their recognition, as more or less definite entities or as conspicuous evidences of deeper and more general disorders. The systems have, however, been based for the most part upon single outstanding features, such as the locality or individual character of the tumors or upon the alterations of the circulating white corpuscles. Constitutional effects, such as anemia or cachexia, have been, by some, included among the criteria for the separation of otherwise similar diseases. As one reviews the history of our knowledge, through the work of such men as Wilkes, Virchow, Kundrat, Trousseau, Reed, Sternberg, Türk, McCallum, Ewing and Webster, there is an evident paucity of criteria upon which a diagnosis can be reached in any given case, especially where one has to do with the zone between true leukemia and sarcoma, conditions which have presented a bewildering number of varieties. There has been too great a tendency to make subdivisions upon the basis of one or two instances which vary in minor factors. Sternberg,[4] in his chapter in Marchand and Krehl's *Handbuch der Allgemeinen Pathologie*, while describing many unusual conditions in beautiful detail, confuses as much as helps by offering so many explanations and possibilities. One also asks, when studying the whole subject, if there be no systematic clinicopathological basis upon which a definite classification can be made. At present, this question must be answered in the negative, especially since no data of dependable worth as to etiology are at hand. Up to about ten years ago the progress depended entirely upon studies of clinical and necroscopical character. Since then, bacteriological and parasitological data have been accumulating, albeit with small definite results, and greater attention has been paid to the bioscopical diagnosis by adenectomy and the results of roentgen-ray treatment. This history having accumulated, it is not without hope that we may look forward to a classification of lymph-gland enlargements which will enable the clinician to apply to a given case some rules for diagnosis, therapy

and prognosis. It is in this direction that we offer the results of our clinical and pathological studies of upward of one hundred cases, an analysis of which, when combined with the experiences given in the literature, has suggested that we venture a classification based upon physical examination and pathology. The very fact that so many classifications have been offered is evidence that no unanimity exists relative to the proportionate value to be given to each of the criteria presented by cases of adenopathy, a state of affairs which throws us back upon a pathological basis. The clinical features are too variable to allow quantitative values to be assigned them so that a mathematical formula, such as is used in botany, cannot be employed unless one had a really enormous number of cases reported in identic manner from which percentage figures could be quoted. Since this does not exist, the adoption of an acceptable pathological classification permits the preparation of a table of a few definite clinical characters and a number of others with a high degree of probable value.

Lymphatic tissue is distributed in the body as illy outlined lymph-cell collections in organs and in the bone-marrow, as solitary and agminated lymph follicles such as exist in the intestinal wall, as lymph nodes, and as the spleen. The first has no special architecture, its elements being only small lymphatic mononuclears closely packed and apposed or separated by delicate fibrils. Solitary and agminated follicles possess an orderly arrangement of central germinal area and a major part consisting of adult lymphocytes. Indefinite cords and sinuses may occupy the spaces between the follicles proper, the whole being surrounded by some condensation of tissue, but not by a marginal sinus and fibrous capsule. Lymph nodes, unlike the foregoing, are accummulations of lymph cells arranged in an apparently purposeful manner and with an architecture of practically identic character throughout the body, varying only in quantitative sense. Whereas they are simple in construction in the intestinal wall, the regional chains and the plexuses around the hilum of viscera are quite definitely arranged, apparently to care for drainage of the area in which they lie. The spleen is, indeed, only a quite complex lymph or hemolymph node, its lymphoid character being supplemented by blood spaces and its activities being more closely associated with the blood than those of its relatives, disseminated lymphatic bodies. The spleen is peculiar also in being often involved in the diseases of lymph nodes, while these latter are not so frequently altered in diseases originating in the larger organ, such as a primary splenomegaly. The features that concern the present study most directly are the elements comprising the lymph node and the architectural relations they bear to one another. Without going too deeply into histology, it is necessary, however, to discuss the units of cellular construction.

There are three elements involved in the make-up of a node, which are peculiar to it—the lymphoid cells, endothelial cells of the sinuses and perivascular spaces and the reticulum cells and fibers. There are constantly present, however, structures which belong to the so-called myeloid series, polynuclear neutrophiles and eosinophiles, and large mononuclears comparable to the formative cells of the bone-marrow and believed to be the forerunners of polynuclear varieties. Some of these three types are doubtless deposited by the circulating blood. Certain observers have wished to see myeloid tissue in lymph nodes, a view which would explain the presence of these cells upon the basis of local production. Since, however, the diseases of lymphatic nodes never express themselves with alteration of myeloid cells but of the lymphoid series, and since myeloid alterations are so definitely associated with bone-marrow changes, it is not necessary to discuss further for our purpose the academic question of the existence normally of differentiated marrow cells in the lymph nodes. When polynuclear cells are present, there is usually other evidence of inflammation and when myelocytes and promyelocytes are found they can be explained by other lesions of bone-marrow disease.

The first essential elements of the lymph nodes are laid down to form groups called follicles, composed of small mononuclears, apparently growing from larger cells of generally similar character which lie in the center of the group. Here also one finds a small bloodvessel with circumferential endothelial cells. The small mononuclears are extended from the follicles in strands or cords, which are separated from one another by spaces—sinuses, lined by cells apparently of the endothelial series, since they behave like such cells. These sinuses have a delicate network of fibers, within which lie mononuclears, polynuclears and red blood cells.

The framework of all these structures is a delicate reticulum, fitted with stellate cells, some of which have a large, almost vesicular nucleus, and a more compact fibrous tissue with elongated nuclei, which seems to emanate from the large trabecula and from the bloodvessels. There is some question as to whether the reticulum can produce all the fibers seen in certain lymphadenopathies, there being the idea in many quarters that the true fibrous tissue of the gland supplies all this. Our own view is that the reticulum is certainly responsible for much of the fibrosis in early Hodgkin's disease since fine fibrosis is found well developed in the follicle when the Reed cells are beginning along its edge. This delicate supporting tissue is more distributed in the gland than is the coarser connective tissue. It is an important part of the minute construction of lymphosarcoma. For these reasons, we shall write of the supporting tissue as reticulum and imply all the fibrous elements of the lymph node.

The bloodvessels do not seem to undergo very specific changes

during the development of pathological lesions in lymph nodes or at least they do not assume any peculiar character indicative of one or another condition. The capsule and larger trabecula, the coarse mainstays of the node, are for the most part passive and, with few exceptions, fail to participate actively in morbid lesions.

The elements that concern the study of lymphadenopathy are, therefore, lymph cells in their peculiar arrangements, endothelial cells and the reticulum to which may be added units not intrinsically part of lymphatic tissue, the myeloid cells.

The material at our disposal for this study consisted of 65 diagnostic adenectomies upon thoroughly studied and tabulated cases, from 5 of which a second gland was also excised, 10 autopsies and 18 partly tabulated cases, from which glands were submitted for study. These pathological preparations were studied according to the type or types of cells that predominated in the process, the relation of these cells to each other and to the normal architecture. From such a study, it developed that certain groups of preparations were formed because of the similarity of cellular components and collections comprising them and because of the retention or destruction of normal architecture. Starting from these groups, we constructed a scheme based upon changes in each one of the component elements of lymphatic tissue accordingly as they were in normal or abnormal number, in normal or abnormal location and arrangement. The behavior of the various elements, described in a general manner in the following paragraph, was actually traced in our preparations and the principles laid down can be applied to any given section.

The particulate unit of lymphatic tissue, the small lymph cell, being most important, changes in its number, type and arrangement are the first considerations. Reduction of the number of these cells is rare and only seen with general atrophy, as in senility. We may dismiss at this point all hypoplasias and atrophies within lymph nodes, since the disappearance of the whole or parts is not common and of no significance in the diseases to be discussed. Some elements, apparently atrophic, may be merely overshadowed by increase of others.

The principal change in the number of lymph cells, an increase or hyperplasia, constitutes the most important single feature in these glands. This may be a simple orderly process with retention of normal relationships or it may be excessive and destructive of architecture. The absolute increase is independent of the proportion of small mononuclears in the cords and outer zones of the follicles to the larger cells in the follicular centers, the so-called lympho-blasts. No definite value of classification can be placed upon the relation of these two forms, except in so far as the follicular architecture is retained or lost. It would seem, however, that in hyperplasia under the influence of acutely or continuously acting

stimuli as in inflammation, the follicular center with its large pale cells and a mononuclear zone of considerable width are retained in recognizable form. Aside from these two types, there is the plasma cell, almost certainly a derivative of the lymphocyte.

Hyperplasia of these elements in orderly arrangement expresses an obvious attempt to retain approximately normal architecture. When the identity of the follicle and cords is lost, it implies that restraint of growth is lost. To the first type of hyperplasia we apply the term "restrained" growth, to the latter "unrestrained" growth. The latter may go on within the confines of the glandular capsule, or it may penetrate the latter. According to the rules of pathology, the malignancy of any excessive growth is directly proportionate to the degree of departure from normal positions and arrangements. So, too, the advent of new forms of cells increases the abnormality and malignancy, using this term as indicative of the inability to return to normality. However, these changes must be not only quantitative and qualitative, but they must be uniform and sustained.

The size of cells of the lymphatic series is of some help in deciding the activity of the process locally, but cannot be used as a final criterion. The adult cells in normal positions are of the usual size of lymphocytes, but this size may be retained when all architecture is lost.

In "restrained" hyperplasia cells of both lymphocytic and lymphoblastic proportions are usually present; but in certain cases of sarcoma we have found areas, in close proximity, made up wholly of large and small cells. Sometimes the large cells approach in size that of endothelial or reticulum cells. Identification has been made by us upon the basis of other cellular relations and the usual staining reactions; the Schridde granule method has failed us entirely.

Alterations in the endothelia follow the lines given for the lymph cells, increase in normal positions or excessive disproportionate multiplication. Their proliferation along sinuses or about blood-vessels may make them conspicuous and confuse the picture, but their relationship with adjacent tissues is not lost. If multiplication be unrestrained, as in endothelioma, the sinus or perivascular space is so distorted and crowded that adjacent tissues are compressed and may lose all identity. Ewing's description and photographs have been exactly duplicated in some of our cases. Certain of the reticulum cells may also either engage in the process or be involved by it and become indistinguishable from endothelia. Giant forms of three, four or more times the size of normal endothelial cells, are occasionally encountered in both normal and abnormal locations; these may be multinucleated and phagocytic.

The supporting tissue, both reticular and fibrous, seems to be susceptible to the same character of change as one can follow in

the foregoing two elements. On some occasions, it would appear that the reticulum is hyperplastic, on others the connective tissue, the former usually giving rise to fine fibrosis at least at first, the latter, to coarse strands. We think that both are involved in general fibroses of lymph nodes, since we have been able to find fibroglia fibrils very early in true Hodgkin's disease. The behavior of the reticulum and connective-tissue cells is, however, important. When undergoing hyperplasia, the nuclei of these cells may swell to very large size and become what is called endothelioid. Such cells are usually laid along fibers or in small bundles; occasionally they seem to lie in lacunæ. On other occasions, spindle cells may be found in small groups or strands, apparently in active growth; such areas give the impression of a malignant change and this, indeed, may at times be actually what is progressing.

Aside from these changes in elements peculiar to lymph nodes, there may be increase of the adventitious myeloid cells either diffusely or in groups. The arrangement of such increase is not significant unless the polynuclears be aggregated into abscesses. Still another new structure may be found in diseased nodes—the foreign body giant cell. Its exact origin is no more settled here than elsewhere, but there is an abundance of the cells reputed to be its forerunners.

As has already been indicated, and repeated here for consecutiveness, the capsule and larger trabeculæ do not seem to participate actively in diseases of lymph nodes, except perhaps in chronic fibrosis, under which condition hyperplasia may be simple and restrained or destructive of architecture; it may also extend to the tissues about the gland. These tissues are secondarily involved in many conditions.

Degenerative lesions in lymphatic nodes are roughly divisible into those due to the disease virus and those the result of restriction of food supply. Their exact character, with the possible exception of caseation, is not peculiar to any of the recognized morbid states and has not served as a reliable criterion for separation. Local degenerations, to which the term necrosis may apply collectively, are common and because they are gross in some instances, fine in others, and both in still others, they have served as minor distinguishing features.

The foregoing explanation of the basic changes in the histology of the lymph nodes illustrates how each one of the structural units may increase independently. If they were to do so consistently and be combined with uniform clinical expressions, classification would not be so difficult. Sometimes homogeneous hyperplasia of one type does occur and is combined with a definite gross pathology and clinical picture. Under such circumstances, the general grouping is simpler than when several structural elements are involved.

TABLE I.—DESCRIPTIVE OF CHARACTER OF CHANGE IN THE LYMPH NODES BASED UPON NAMES AS THEY APPEAR IN GENERAL USE AND FROM WHICH THE FIFTEEN VARIETIES WERE SELECTED AS TYPES.

Character of pathological change.	Clinical character.	Pathological group.	No.	Specific varieties.	Association.
Hyperplasia	Benign	Lymphoma	1	Lymphoma Status lymphaticus	....
			2	Lymphadenoma	....
			3	Glandular fever (and acute leukemia)	....
	Malignant	Leukemic	4	Leukemia	With 5.
			5	Aleukemia or generalized lymphomatosis	With 4 and 6.
		Neoplastic	6	Leukosarcoma	With 5.
			7	Lymphosarcoma	With 10 and 11.
			8	Reticular sarcoma	With 10 and 11.
			9	Endothelioma	....
Neo-inflammatory	Malignant	Lympho-granuloma	10	Cellular	With 7 and 8.
			11	Fibrous	With 7 and 8.
Inflammatory	Benign	Adenitis	12	Simple	....
			13	Purulent	....
			14	Tuberculous	With 11.
			15	Syphilitic	....

TABLE II.—THIS SHOWS THE CHARACTER OF HISTOLOGICAL CHANGE IN EACH OF THE TYPES SHOWN IN TABLE I. PLUS SIGNS INDICATE THE PRESENCE OF THE CHANGE AT THE HEADING OF THE COLUMNS, AS A DISTINCTIVE CHARACTER; NO SIGN MEANS ABSENCE THEREOF. WHEN PLUS AND MINUS SIGNS ARE COMBINED THE UPPER INDICATES THE PRESENCE OR ABSENCE, AS A RULE, THE LOWER AN OCCASIONAL FINDING.

	Lymphoid elements.						Endothelial elements.			Reticular elements.					Special features.					
	Restrained hyperplasia.	Follicular centers preserved.	Unrestrained hyperplasia.	(a) Within node.	(b) Through capsule.	New types of cells, plasma.	Restrained hyperplasia.	Unrestrained hyperplasia.	Giant forms.	Restrained hyperplasia.	Fine fibrosis.	Coarse fibrosis.	Unrestrained hyperplasia.	Endothelioid types.	Polynuclear neutrophiles.	Eosinophiles.	Giant cells, foreign-body type.	Gröss necroses.	Fine necroses.	Capsular adhesions.
1	+	+																		
2	+	+					+													
3	+	+																		
4			+	+																
5			+	+																
4			+		+					+	+									+
7			+		+	+				+	+							+	+	+
8													+					+	+	
9								+	+			+	+							+
10	+					+	+		+	+	+			+	+	+			+	
11	+					+	+		+	+		+	+	+	+	+		+	+	+
12	+	+					+			+	+			+	+	+	+		+	
13	+	+					+			+				+	+			+	+	+
14	+	+				+	+		+	+		+		+	+	+	+	+	+	+
15	+	+				+	+			+	+			+	+	+	+		+	

NOTE.—These charts were made to be read directly across the

The cases of pure hyperplasia of the different histological elements have been grouped, and their combinations have been classed as they fell together. In constructing such groups, we have assumed pure hyperplasia as an increase of one or another type of cell, benign when restrained, malignant when unrestrained, and inflammation as a mixture of normal and adventitious elements in attempted normal relations. We have, however, been obliged to recognize that certain cases had inflammatory characters yet with abnormal prominence of certain cells that suggested hyperplasia of a disorderly variety; to this group, we have applied the term neo-inflammatory, because it had characters like neoplasms yet was histologically inflammatory also. Curiously enough, this is lymphogranuloma or Hodgkin's disease, long considered by some observers to be tumorous.

To summarize thus far, it may be stated that our material was studied from the standpoint of the histological elements responsible for the enlargement of the lymph nodes and that it is possible to find examples among the diagnostically removed tissue wherein this enlargement was due to hyperplasia of each one of the tissue

TABLE III.—THIS SHOWS THE CLINICAL AND GROSS PATHOLOGICAL FINDINGS IN THE TYPES SHOWN IN TABLE I. *SIGNS DIFFERENT FROM TABLE II.* PLUS AND MINUS SIGNS INDICATE RESPECTIVELY PRESENCE AND ABSENCE OF FEATURE AT HEAD OF COLUMN. NO SIGN MEANS ABSENCE OR INADEQUACY OF INFORMATION. COMBINED SIGNS MEAN THAT UPPER IS THE RULE, THE LOWER OCCASIONALLY HOLDING GOOD.

	Clinical Characters.												Gross pathological characters.					
	Local.	General.	Separate units.	Coherent or coalescing.	Rapid growth.	Slow growth.	Mediastinum involved.	Cachexia.	Softening of tumor masses.	Enlarged spleen.	Circulating lymphoids increased.	Circulating myeloids increased.	Cutaneous lesions.	One principal tumor.	Massed glands.	Single glands.	Visceral infiltrates.	Visceral tumors.	Bone-marrow specifically involved.
1	+	+	+	−	+	−	±	−	−	±	−	−	−	−	−	+	+	−	±
2	+	−	+	−	+	−	−	−	−	−	−	−	−	+	+	−	−	−	−
3	−	+	+	−	+	−	−	−	−	±	+	−	−	−	−	+	±	−	−
4	−	+	+	±	−	+	±	±	−	+	+	−	+	−	±	+	+	−	+
5	−	+	+	±	−	+	±	±	−	±	−	−	±	−	±	+	+	−	+
6	+	−	−	+	+	−	±	+	−	−	+	−	−	+	+	−	±	+	−
7	+	−	−	+	±	±	±	±	−	−	−	−	−	+	+	−	−	+	−
8	+	−	−	+	+	−	±	+	+	−	−	−	−	+	+	−	−	+	−
9	+	+	+	+	−	+	−	−	−	−	−	−	−	±	+	+	−	±	−
10	−	+	+	−	+	−	±	+	−	±	−	+	±	−	−	+	+	+	+
11	−	+	−	+	−	+	+	+	−	+	−	+	±	−	+	+	+	+	+
12	+	+	+	−	+	+	−	−	−	−	−	−	−	−	−	+	−	−	±
13	+	±	+	+	+	−	±	−	+	−	−	+	−	−	+	+	−	−	−
14	+	+	+	−	−	+	±	±	±	±	−	−	−	−	+	+	−	−	−
15	−	+	+	−	−	+	−	−	−	−	−	−	±	−	−	+	−	−	−

lines, but because of their size, could not be set upon one page.

components, in normal or abnormal relations, as a pure and single type of cellular increase or as a mixed hyperplasia made up of several types. The cases presenting a pure type of hyperplasia of each cell were put into groups and combined hyperplasias were grouped as they fell into combination. When the findings were tabulated, Table II, they were found to correspond with the theoretical classification, Table I.

Having arrived at this stage of our work, the names of all diseases of the lymphoid organs as written in books were copied, the total amounting to nearly fifty, from which, by the elimination of undoubted synonyms and meaningless terms, we made a condensed list of twenty-seven. From these we selected fifteen, which we believed to be separate clinicopathological types, between which there were sufficient differences to be distinctive.

These types were made into a table of clinical characteristics, according to our own records and from the literature. The headings of symptoms and signs amounted to about fifty, but from these 13 were selected as being most definite in their informative quality; this group of 13 will be found in Table III. However, the physical signs and symptoms are so variable that very few of them are of final dependability; many have to be noted as both present or absent. The diagnosis of a given case may, up to a certain point, be made by comparing the data with such a chart, but in closely similar clinical pictures the differentiation must be made by diagnostic adenectomy or on the basis of gross pathology. The tables given here are the result of many larger and more elaborate predecessors. That descriptive of the histological changes, Table II, was made first and then fitted with Table I, which is based upon the names of adenopathy given in the literature but selected as representative separate types. Descriptive legends accompany the tables.

Table I has as its first divisions hyperplasia, neo-inflammation and inflammation. Hyperplasia may be benign or malignant, a character perceived equally in clinical course and by histological examination of the tissue when viewed by the criteria discussed in the foregoing pages. Where inflammation is combined with progressive growth, cachexia and with the increase of certain cells beyond their normal position within the node, the whole process tends toward malignancy; such is the condition in lymphogranuloma. Inflammation is benign clinically and in its attempted retention of normal anatomical characters.

Examination of the pathological characters naturally follows the division of clinical behavior. Hyperplasia of lymphoid tissue has long been called lymphoma so that the term is retained, but simple orderly increases of small mononuclears are not necessarily neoplastic. However, this type of hyperplasia does occur in iso-

lated glands, as local tumefactions and as a general process. When intraglandular hyperplasia becomes so excessive that mononuclears are spilled into the blood stream, the process becomes leukemia. Certain cases have a generalized leukemic pathology, yet do not show increased circulating lymphocytes, aleukemic varieties or phases. Hyperplasia of an exaggerated disorderly kind may occur in restricted localities, assuming then a form comparable to tumors; they may be associated with leukemia or free of this character. All these foregoing forms are strictly of lymphocyte origin. In the true sarcomata of lymph nodes, an increase of more than one element is found, both lymph cells and reticulum being hyperplastic. Under these conditions, the trend is away from purity of hyperplasia, but one or another element always dominates the picture. The next group, lymphogranuloma, combines hyperplasia of certain elements, endothelial cells notably, in atypical arrangement, with the addition of pathological anatomy of chronic inflammation, a construction peculiar to lymphatic bodies. Adenitis exists when all elements of nodal architecture are active and are joined by the adventitious cells of the blood. The next column of numbers is added merely for convenience.

The specific varieties used to illustrate the types of change were selected from the list of pathological states, as mentioned above, and because they are believed to be all the principal kinds of lymphadenopathy. There are doubtless gradations between these individuals; there certainly must be between the sarcomata, for now and again one will find a case that will not permit of this nomenclature. Many varieties of lymphosarcoma have been described, notable among which are chlorosarcoma and plasmocytoma.

Lymphoma is intended to cover the hyperplasias left after certain longstanding irritations and in the condition known as the thymicolymphatic state. Lymphadenoma is a term long used to describe many lymph-node enlargements, but we wish to limit its use and to explain here our reason. The term should mean a tumor of lymph nodes, one made up of and like lymph nodes, with their peculiar construction. Other tumors of the nodes soon lose their architecture and are given appropriate names. We have observed what seems to be correctly called lymphadenoma. A man, aged forty years, was struck in the neck by a baseball, following which, three months later, a large nodular tumor developed at the place of injury. No other lymph-node enlargements existed and the man had a healthy mouth without obvious bad teeth. At operation a compound nodal tumor was removed, the microanatomy of which was that of normal lymph node. One year later, when last heard from, he was in perfect health and without a trace of return or extension.

Glandular fever is peculiar in that its acute manifestations are unlike any other condition in the list. It might be related with acute leukemia, which condition may be said to form a connecting link with it and the next disease, leukemia. A diagnosis of acute leukemia has been seriously considered in certain cases of glandular fever. The fever is not included in the tabulation because of the inconspicuousness of the glandular features and ease with which the disease can be separated from the definite lymphadenopathies.

Leukemia proper is self-explanatory. Aleukemic leukemia is the term we apply to pseudoleukemia of Cohnheim, because it is pathologically like leukemia and only separated from it clinically by the inconstancy of hyperlymphocytosis. Ewing's[1] term, systemic lymphomatosis, is satisfactory, but fails to convey the suggestion that the process is histologically like leukemic hyperplasia and that the disease may have phases in which the circulating mononuclears are increased. Leukosarcoma is, according to Sternberg,[4] who first described it, a local leukemic tumor with increased circulatory mononuclears. The typical lymphosarcoma of Kundrat is a mononuclear cell tumor, with fine reticulum and no change in the blood picture. Sarcoma, arising from reticulum or connective-tissue cells, may be either of the round or spindle-cell variety, and when studied microscopically fails to show the purity of the component cells characteristic of sarcomata arising from lymph cells; variability in the size, shape and arrangement of cells is quite typical of these tumors. Endothelioma presents no features of lymphoid tissue within the neoplastic areas, being constructed throughout upon the basis of large cells with loose nuclei.

Hodgkin's disease may be divided into the cellular and fibrous varieties, but whether these are strictly different or only stages of the course of disease is as yet unsettled. We believe we shall be able at a later time to show their individuality (see Ziegler).[8]

The types of adenitis listed in the table are clinically and etiologically different, but analysis by the criteria already discussed does not serve to separate them very sharply.

The column of association is meant to indicate how these various individual conditions are related to one another or how they may transmute. The relation of leukemia and aleukemic leukemia has already been discussed, as has their connection with leukosarcoma. The association of sarcoma with Hodgkin's disease is credited by Ewing[1] upon the basis of work of Welch, Karsner and Yamasaki; we have not had occasion to see it. Lymphogranuloma and tuberculosis are noted as related to one another in deference to the opinion of many writers; our tests have failed to establish the tuberculous basis of Hodgkin's disease.

Having disposed of the groupings in Table I, we may now see how they will fit into the classification from the standpoint of

changes in the histological elements on Table II. The tabulation is made according to the changes described as taking place in lymphoid, in endothelioid and in reticular elements with the addition of special features, such as myeloid cells, giant cells and necroses. A survey of the whole chart reveals at once that there are rough groupings which correspond with the grosser subdivisions of the theoretical and clinical sections. The purity of the first and second gross subdivision is carried forward and is consistent in nearly every particular. When one reviews the neoplastic division, it is evident that more kinds of tissue are involved and that the four specified varieties fall into three general groups. The first embraces the two sarcomata from lymphoid cells (Nos. 6 and 7), the second is represented by reticulum sarcoma and the third by endothelioma alone.

Inspection of the tabulated histological characters of lymphogranuloma reveals that they are distinct from the foregoing varieties, but possess much in common with definite inflammations in the next subdivision. These latter are not greatly different, except the syphilitic, and, indeed, their variations may probably all be explained upon the basis of chronicity.

Section III of the table is an analysis of the clinical and gross pathological features considered to be most distinctive of these lymphadenopathies and most helpful in diagnosis. The twenty headings are selected from seventy tabulated on a large table. However, these are not all of equal value and do not individually possess the same relative value down the list of fifteen specific varieties. Conspicuous in this inconsistency is the rate of growth. What would be rapid for Hodgkin's disease would be slow for purulent adenitis; a rapidly developing sarcoma would be slow for glandular fever. Yet, it is necessary to contrast aleukemic leukemia and leukosarcoma, reticulum sarcoma and endothelioma, acute and chronic Hodgkin's disease. We wish it known that this has but a relative value and that we are aware of it. Many of these features are variable enough in a clinical case to require both a positive and negative sign to indicate that they may or may not be present. The order in which they are placed is that of greatest percentage of positive characteristics. Some of the diagnoses exhibit features requiring a positive entry in two opposed characters. The relative importance of each of these criteria is impossible to evaluate at present because there is no uniformity with which each of the varieties display their special characters as indicated by so many plus-minus signs, and because there is no unanimity of opinion as to the most important ones. These remarks will be emphasized by a review of the table of clinical characters in which it will be seen that no distinct grouping occurs as could be found in the histological analysis. There is a rough grouping of the benign and leukemic hyperplasias and of the small

mononuclear neoplasms, but distinctive subdivisions do not appear. The most important features we believe to be whether the growth is local or general, whether separate or coalescing, whether the spleen is enlarged or not and the state of the circulating leukocytes. The table serves to show that, up to a certain point, a diagnosis may be approximated, but that the settlement of the question must remain for gross or microscopic anatomy to settle. This is especially true of the aleukemic leukemias, neoplasms and granulomata.

Gross pathology, as seen by operative removal of a tumor or at autopsy, is of some value. Or this gross pathology may be discovered by clinical means, among which the roentgen ray is included. Thereby it may be established that the cervical or axillary mass is solitary, a discovery favoring the lymphoid and reticular sarcomata. Like the clinical data, these features in gross pathology have a relative value and are to be used in combination with bedside information. The most important at autopsy would seem to be the existence of a single tumor, the presence of visceral infiltrations and the changes in the bone-marrow. When organs contain infiltrates, it would seem to indicate that the cells of the original process are circulating, or that the visceral nodes have been stimulated to hyperplasia.

Having presented the data acquired by a study of lymph nodes excised during life from cases of lymphadenopathy, combined with an analysis of their clinical character, and having described a theoretical system based upon what is believed can happen in the anatomical elements of lymphatic tissues in terms of the names applied clinically and pathologically, it seems well at this point to define clearly the meaning and limits of each one of the fifteen types we believe to be separate.

The term lymphoma indicates a tumor of lymph cells. The name is retained because of general use, but is restricted in our work to pure orderly hyperplasias, such as are seen in chronic intoxication and in the lymphatic status. Exemplifying the former of these conditions, may be cited the lymphatic enlargements accompanying toxic goiters. This whole conception implies either a local or general increase of discrete glands or of visceral lymphoid collections without distinctive lymphocytosis. The purity of lymphatic hyperplasia in this first group and in the third, the acute forms behaving like acute infectious diseases, is the dominant pathological feature. Glandular fever is, however, combined with a definite circulating mononucleosis. It forms the first of the hyperplasias that seem to be peculiar and restricted to lymphatic tissues and merges with acute leukemia into a group connecting with the chronic form. As a clinical feature, lymph-nodal enlargement is definitely less conspicuous than it is in long-standing diseases, and there is an increase of circulating lymphoid

cells. Lymphadenoma, a compound tumor retaining nodal architecture, must be a rare condition; our case has been cited.

Leukemia is a condition diagnosed clinically by the discovery of an increase of circulating mononuclears. It is a systemic disease characterized by generalized lymph-node enlargement, mononuclear infiltrates in viscera, single or massed glandular tumors usually however, retaining, when *en masse*, their individual outlines. The disease is essentially slow in course and marked by irregular remissions. The spleen is usually enlarged. Histologically, the hyperplasia is pure in type and, although in the late stages destructive of intraglandular architecture, does not involve the capsule and adjacent tissues. Aleukemic leukemia or systemic lymphomatosis is exactly the same process, beginning more insidiously and not associated with leukemic blood. There may be subleukemic phases, however, especially just ante mortem (Sternberg).

Leukosarcoma is defined by Sternberg as a local invasive tumor composed of lymphoid cells associated with a definite but not constant mononucleosis. The fact that it is primarily local differentiates it from the foregoing two varieties. It may become generalized as a late development.

Lymphosarcoma is primarily a local tumor, practically always disseminated before death. The variety found in the intestinal wall may remain local and be amenable to surgical treatment. This tumor differs from leukosarcoma in the absence of circulating mononucleosis, the implication of both lymphoid and reticulum cells, the presence of a fine intercellular fibrosis and a tendency for gross and fine necroses to appear. It was attempted to discover from our sections distinct differences in the vascular supply to account for these necroses, but no result could be achieved.

Endothelioma may be a local tumor or the growth may involve many glands, which, however, tend to remain discrete. The chronicity of the tumor is a marked character. Visceral involvement is rare. Histologically, the peculiarity of the growth lies in the development of islands or strands of endothelial cells, sometimes growing through lymphoid tissues, sometimes surrounded by non-specific fibrous tissue which is disorderly in arrangement.

Lymphogranuloma, or Hodgkin's disease, although usually expressing itself as a local growth, must nowadays be considered as a systemic affection. It can be defined as an enlargement of lymph nodes occurring most often in young adults and adolescents, without mononucleosis, but often in the early stages with polynucleosis, with involvement of the spleen, with a tendency for internal masses to develop, and with a histological lesion, consisting chiefly of inflammatory changes combined with a prominence of large mononuclears suggesting unrestrained neoplastic activity. Its varieties depend upon whether the glands remain isolated or

grow into coalesced tumor masses; the rate of growth, this being more rapid with discrete nodes; the degree of fibrosis, which is greater in the tumor-forming type; the presence of foreign body giant cells and gross necroses, both of which are usually absent from isolated, discrete nodes and present in large fibrous tumors. Large mononuclears, with one compound nucleus or with numerous nuclei, those arranged parallel to the cell wall, are strongly supportive of this growth. Langhans giant cells are occasionally but not necessarily present; they are much more directly indicative of tuberculous adenitis.

Adenitis is that state of lymphatic tissue change in which all elements, normal and adventitious, participate in the process. Its varieties, as noted in Nos. 12 to 15 inclusive, depend upon the nature of the cause and upon the prominence of certain incidental factors. They vary also in terms of chronicity. The simple form differs from the purulent in the rate of growth, the degenerations and the prominence of polynuclears. Tuberculous adenitis need confuse only in respect to Hodgkin's disease, with which it has many similarities. The variety of the latter ascribed to tuberculosis by Sternberg cannot always be differentiated by histology, and a decision must be left to bacteriology. Ordinary cases of tuberculosis are to be distinguished from non-tuberculous lymphogranuloma by the evident attempt at the retention of architecture, the formation of tubercles or at least of foreign body giant cells in granulation tissue and the inconspicuousness of the so-called Reed cells in the variety certainly due to the Bacillus tuberculosis.

The small, isolated, firm, slowly growing glands in the adenitis of syphilis are noteworthy for the dense packing of lymphocytes in approximately normal relations and the fine perifollicular and perivascular fibrosis. Gummata may be present.

Summary. The study of the material upon which we have worked, especially the anatomy of excised lymph nodes, permits a grouping of cases based upon the type of cell primarily responsible for the enlargement. The groups into which the cases fall correspond first to a theoretical system, based upon what is possible when the component parts of lymphatic tissue become hyperplastic, and second, to types of pathological characters and clinical behavior. Such a classification, although founded upon work which has adduced no essentially new facts, establishes more firmly the nature of lymphadenopathies, since it is based upon tissues removed during life—therefore, during the natural activity of the morbid process. It may help to formulate a simpler scheme for these illy understood entities, and to reduce the number of terms employed in describing them. No system can reach all variants from a type, especially in these diseases where so many confusing individual cases appear. The work also illustrates that certain of the leukemic and neoplastic forms of lymphadenopathy cannot be diagnosed solely upon

clinical signs, but that data acquired by adenectomy must be available for this purpose.

BIBLIOGRAPHY.

1. Ewing: Neoplastic Diseases, Philadelphia, 1921.
2. McCallum: Text-book of Pathology, Philadelphia, 1920.
3. Nageli: Leukemia, Vienna, 1913.
4. Sternberg: Marchand u. Krehl Hand. d. Allg. Path., 1912, **2**, 187, *et seq.*
5. Türk: Wien. klin. Wchnschr., 1899, **40**, 985.
6. Türk: Berl. klin. Wchnschr., 1903, **39**, 1073.
7. Webster: Johns Hopkins Hosp. Reports, 1921, No. 3, vol. **20**.
8. Ziegler: Die Hodgkinsche Krankheit, Jena, 1911.

A CONTRIBUTION TO THE PHYSIOLOGY OF THE PINEAL BODY.

By Yositame Izawa, M.D.

OKAYAMA.

(From the Anatomical Laboratory of the Okayama Medical School, Okayama, Japan.)

The problem concerning the function of the pineal body is not yet definitely decided. The importance of the pineal body is, however, clear from the fact that its tumor is often attended by "pineal disorder," namely premature development of primary and secondary sexual characters.

A Historical Review of Experimental Results. Howell,[24] the first to try the intravenous injection of pineal extract, records that its effect upon the blood-pressure is inconstant. Von Cyon[9] believes, as a consequence of the intravenous injection of pineal extract and of electrical stimulations, that the pineal body plays a role in preserving certain inorganic substances as organic compounds, and moreover, that it regulates the flow or cerebrospinal fluid in the third ventricle. In 1909 Dixon and Halliburton[12] examined the effect of pineal extract, but their results were negative so far as the blood-pressure, heart rate, respiration, the volume of the intestine, kidney and urine secretions are concerned. Jordan and Eyster[28] observed transitory diuresis and glycosuria after the injection of the pineal extract; and Otto and Scott[40] report similar results. Horrax[25] states that intravenous injections of pineal extract would cause a constant but slight fall in blood-pressure.

According to Dana and Berkley,[10] as well as to McCord,[33] a prolonged administration of the pineal drug brings on a relatively rapid growth of the animals subjected to the experiments. Although no serious effects were observed in the animals subjected to the

administration of the pineal drug, the extirpation of the pineal body caused striking results.

Biedl[6] and Dandy[11] subjected dogs, and Exner and Boesse,[14] rabbits, to pinealectomy, but they obtained no affirmative results. On the other hand Sarteschi[44] succeeded in getting positive results after pinealectomy. In 1913, he recorded that guinea-pigs and puppies subjected to the operation revealed an increase in body weight and in the size of the testes, but no change in the other endocrine glands. In papers by Foa[16] we find that pinealectomized cocks showed a hastened maturity and crowed earlier than controls. Besides he observed a marked hypertrophy of the comb and testes in the cocks that were operated on, there was no change in the case of hens. The fact that pinealectomized rats showed an increase in weight of the testes was also recorded by him. These observations were on the whole affirmed by Zoia.[52] Recently Horrax[26] has obtained remarkable results after pinealectomy in many guinea-pigs and rats. His conclusions are as follows: "Pinealectomized male guinea-pigs showed a hastened development of the sexual organs, manifested before maturity by a relative increase in size and weight, both of testes and seminal vesicles, over control pigs of the same litter. Histologically the testes and seminal vesicles of these animals, if taken before the age of sexual maturity, showed a more advanced physiological state than controls.

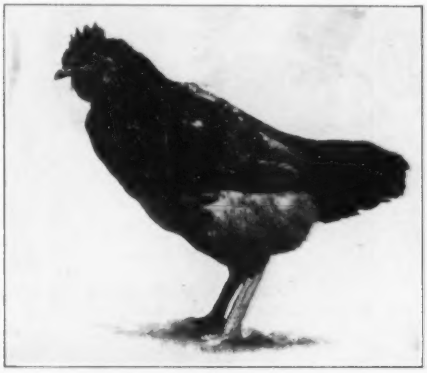
Pinealectomized females appear to show a tendency to breed earlier than controls of the same age and weight."

Therefore it appears to be established that in pinealectomized young males the body weight and the size of the testes (in the case of cocks, the combs, and in the case of guinea-pigs, the seminal vesicles also), grow much more rapidly than in control animals. On the contrary no considerable change has been reported as yet in the case of females.

In order to ascertain the function of the pineal body, both in young males and young females, I have undertaken the extirpation of the pineal bodies in many chickens, males as well as females. In all, I performed the operation of pinealectomy on 36 chickens ranging from four to five weeks of age. Besides these chickens 11 others of the same age and weight as those operated on were used for comparison.

Method of Operation. The operation was conducted with careful aseptic precautions. The unanesthetized animal was wrapped with sterile gauze, and after shaving and applying of tincture of iodine, the skin on the posterior end of the skull was cut along the median line. Then the bone was so far removed as to allow the exposure of the posterior portion of the superior longitudinal sinus, where two lateral sinuses join. After a transverse section of this portion of the sinus had been made with small scissors, without ligating it, the under stump of the sinus wall was drawn out, which

manipulation permitted an exposure of the pineal body. This was grasped firmly with a small pair of forceps and gently pulled out, caution being taken not to snap it in two but to remove it whole. After the extraction of the organ, which was accompanied by a somewhat serious hemorrhage from the sinus, the wound was closed by suture of the skin. In the control animals also, the skull was opened in like manner, but the wound was immediately closed without opening up the dura mater.



A

B

FIG. 1.—Cocks (Case I), aged two hundred and ten days, one hundred and eighty-two days after operation. *A*, pinealectomized cock; *B*, control.

Postoperative Observations. Most of the pinealectomized chickens died shortly after the operation from intracranial hemorrhage. Only 4 (3 males and 1 female) survived the operation for any length of time. These were fed under the same conditions as the

control animals and the effects observed. Compared with the control chickens, the pinealectomized animals showed a retarded growth for a few weeks following the operation, but about a month later they began to grow more rapidly than the controls (with the exception of 1 male chicken in which the pineal body had not been entirely removed, as was revealed by the autopsy that was

A

B

FIG. 2.—Cocks (Case II), aged two hundred and fifty-one days; two hundred and twenty days after operation. *A*, pinealectomized cock; *B*, control.

made later). Their body weight became greater and their legs longer than in the case of the controls (Figs. 1 and 2). In the 2 males whose pineal bodies were completely removed, the rapid development of the comb and the premature crow deserve special attention and they gave evidence of sexual instinct from thirty-one to fifty days before their controls. (See Table I.)

Autopsy Findings and Histological Examinations. Of the animals that survived, the pineal body was completely removed in 3 chickens, 2 males and 1 female, as the autopsy testified. One of the males lived one hundred and eighty-two days, the second two hundred and twenty days, and the third one hundred and thirty days after the operation, whereupon all of them were killed, together with the controls. After weighing or measuring, the endocrine organs were fixed with formalin and sections of them stained with eosin-hematoxylin.

TABLE I.

	Case I (♂)		Case II (♂)		Case III (♀)	
	Pinealectomized chicken.	Control.	Pinealectomized chicken.	Control.	Pinealectomized chicken.	Control.
Age of animal on day of operation in days	28	28	31	31	35	35
On the day of killing the animal:						
Age in days	210	210	251	251	165	165
Body weight in gm.	1820	1200	1950	1600	1400	1050
Weight of testes in gm.	14.3	1.49	18.0	7.0		
Relative weight of testes in gm. to a kg. of body weight	7.85	1.24	9.7	4.3		
Weight of ovary in gm.	...	...	...	...	1.12	0.5
Length of Fallopian tube in cm.	...	...	...	...	16.0	9.0
Weight of comb in gm.	5.0	0.7	16.0	2.5		
Weight of hypophysis in gm.	0.012	0.015	0.012	0.013	0.01	0.0085
Relative weight in gm. to a kg. of body weight	0.0060	0.0125	0.0061	0.0081	0.0071	0.0080
Weight of parathyroids in gm.	0.0078	0.0078	0.0090	0.0110	0.020	0.015
Relative weight in gm. to a kg. of body weight	0.0042	0.0058	0.0046	0.0058	0.0142	0.0141
Weight of thyroid in gm.	0.09	0.065	0.1	0.085	0.12	0.05
Relative weight in gm. to a kg. of body weight	0.049	0.054	0.051	0.053	0.085	0.042
Weight of suprarenal in gm.	0.16	0.182	0.15	0.135	0.135	0.085
Relative weight in gm. to a kg. of body weight	0.081	0.151	0.077	0.084	0.096	0.081
Weight of thymus in gm.	2.75	1.7	3.1	2.7	1.85	1.9
Relative weight in gm. to a kg. of body weight	1.51	1.41	1.58	1.7	1.32	1.89
Weight of pancreas in gm.	3.1	3.25	4.0	3.8	2.8	2.82
Relative weight in gm. to a kg. of body weight	1.70	2.7	2.0	2.3	2.0	2.08
Weight of bursa fabricii	2.10	2.0	1.8	1.9	1.5	1.7
Length of left femur in cm.	10	9	11	9	8.0	8.0
Length of left tibio-tarsus in cm.	13	10.5	14	11	9.0	8.5
Length of left tarso-metatarsus in cm.	11	9	12	10	8.5	7.9
Age of animal on the day when it crowed the first time, in days	185	*	205	240		

* Never crowed.

control animals and the effects observed. Compared with the control chickens, the pinealectomized animals showed a retarded growth for a few weeks following the operation, but about a month later they began to grow more rapidly than the controls (with the exception of 1 male chicken in which the pineal body had not been entirely removed, as was revealed by the autopsy that was

A

B

FIG. 2.—Cocks (Case II), aged two hundred and fifty-one days; two hundred and twenty days after operation. *A*, pinealectomized cock; *B*, control.

made later). Their body weight became greater and their legs longer than in the case of the controls (Figs. 1 and 2). In the 2 males whose pineal bodies were completely removed, the rapid development of the comb and the premature crow deserve special attention and they gave evidence of sexual instinct from thirty-one to fifty days before their controls. (See Table I.)

Autopsy Findings and Histological Examinations. Of the animals that survived, the pineal body was completely removed in 3 chickens, 2 males and 1 female, as the autopsy testified. One of the males lived one hundred and eighty-two days, the second two hundred and twenty days, and the third one hundred and thirty days after the operation, whereupon all of them were killed, together with the controls. After weighing or measuring, the endocrine organs were fixed with formalin and sections of them stained with eosin-hematoxylin.

TABLE I.

	Case I (♂)		Case II (♂)		Case III (♀)	
	Pinealectomized chicken.	Control.	Pinealectomized chicken.	Control.	Pinealectomized chicken.	Control.
Age of animal on day of operation in days	28	28	31	31	35	35
On the day of killing the animal:						
Age in days	210	210	251	251	165	165
Body weight in gm.	1820	1200	1950	1600	1400	1050
Weight of testes in gm.	14.3	1.49	18.0	7.0		
Relative weight of testes in gm. to a kg. of body weight	7.85	1.24	9.7	4.3		
Weight of ovary in gm.	...	...	...	...	1.12	0.5
Length of Fallopian tube in cm.	...	...	...	...	16.0	9.0
Weight of comb in gm.	5.0	0.7	16.0	2.5		
Weight of hypophysis in gm.	0.012	0.015	0.012	0.013	0.01	0.0085
Relative weight in gm. to a kg. of body weight	0.0060	0.0125	0.0061	0.0081	0.0071	0.0080
Weight of parathyroids in gm.	0.0078	0.0078	0.0090	0.0110	0.020	0.015
Relative weight in gm. to a kg. of body weight	0.0042	0.0058	0.0046	0.0058	0.0142	0.0141
Weight of thyroid in gm.	0.09	0.065	0.1	0.085	0.12	0.05
Relative weight in gm. to a kg. of body weight	0.049	0.054	0.051	0.053	0.085	0.042
Weight of suprarenal in gm.	0.16	0.182	0.15	0.135	0.135	0.085
Relative weight in gm. to a kg. of body weight	0.081	0.151	0.077	0.084	0.096	0.081
Weight of thymus in gm.	2.75	1.7	3.1	2.7	1.85	1.9
Relative weight in gm. to a kg. of body weight	1.51	1.41	1.58	1.7	1.32	1.89
Weight of pancreas in gm.	3.1	3.25	4.0	3.8	2.8	2.82
Relative weight in gm. to a kg. of body weight	1.70	2.7	2.0	2.3	2.0	2.08
Weight of bursa fabricii	2.10	2.0	1.8	1.9	1.5	1.7
Length of left femur in cm.	10	9	11	9	8.0	8.0
Length of left tibio-tarsus in cm.	13	10.5	14	11	9.0	8.5
Length of left tarso-metatarsus in cm.	11	9	12	10	8.5	7.9
Age of animal on the day when it crowed the first time, in days	185	*	205	240		

* Never crowed.

As seen in Table I, the development of the sexual organs (testes, ovary, and Fallopian tube) of the pinealectomized animals was most remarkable, as compared with the controls (Figs. 3 to 5). In the long Fallopian tube the voluminous ampullary part was sharply

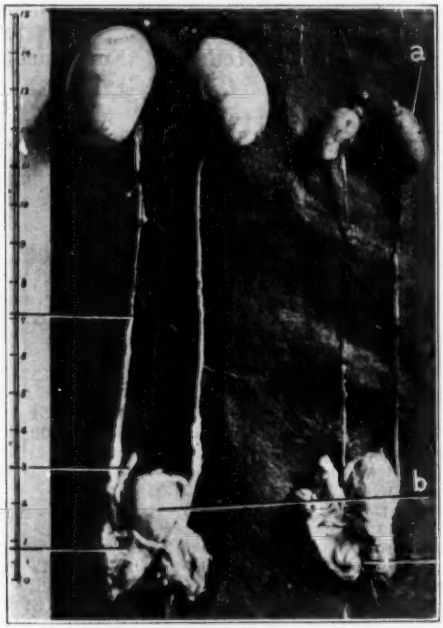


FIG. 3.—Testes of the cocks belonging to Case I. The left, those of the pinealectomized animal; the right, those of the control. *a*, testes; *b*, bursa fabricii.

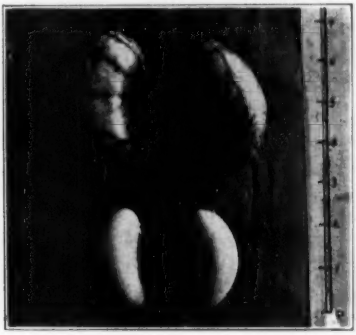


FIG. 4.—Testes of the cocks belonging to Case II. The upper, those of the pinealectomized cock; the lower, those of the control.

contrasted with the slender upper portion, while the same tube in the control is not only short but uniformly slender through its whole length (Fig. 5).

Microscopically, the seminiferous tubules were markedly dilated and contained several layers of epithelial cells showing all stages of spermatogenesis (Fig. 6, A). On the other hand those of the controls remained small and were almost filled with a few layers of not yet differentiated epithelium cells (Fig. 6, B).

With regard to the interstitial cells of the testes, they seemed somewhat increased in number in the pinealectomized animals.

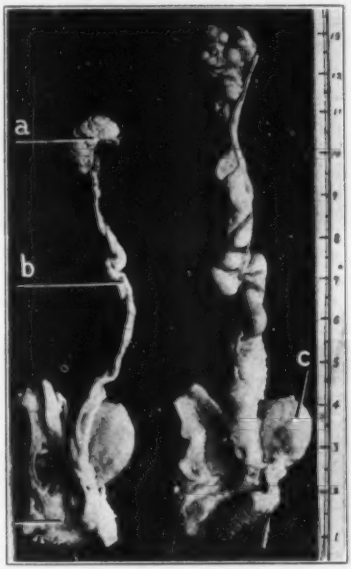
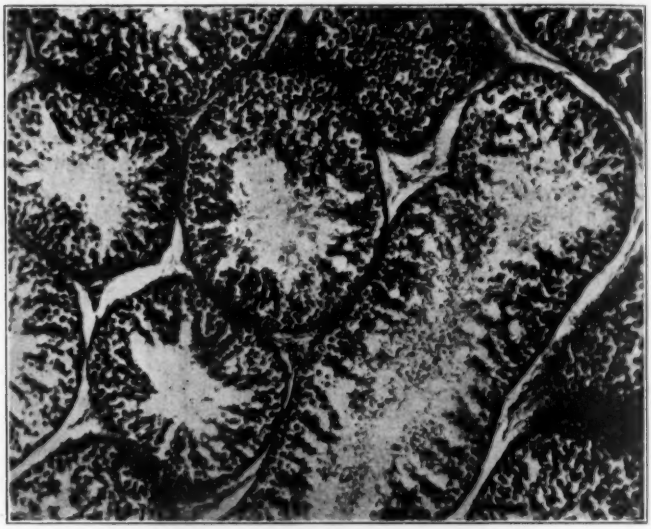


FIG. 5.—Sexual organs of hens, aged twenty-three weeks, one hundred and fifty days after operation (Case III). Right, those of the pinealectomized hen; left those of the control. *a*, ovary; *b*, Fallopian tube; *c*, bursa fabricii.

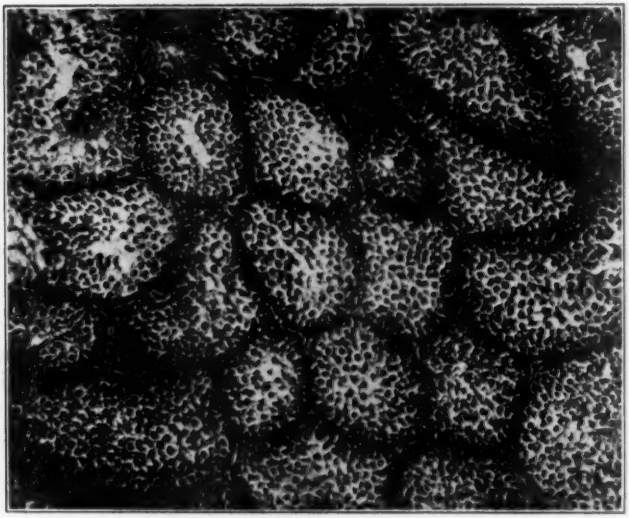
In the section of ovary of the pinealectomized female, well developed follicles measuring more than 390μ were often met with, some of them projecting above the surface of the ovary, while the same organ of the control contained no such follicle, the largest being less than 100μ (compare Fig. 5).

As to the other endocrine organs, it may be said that the difference between the pinealectomized and control animals was slight or entirely absent.

The pituitary bodies of the pinealectomized chickens remained normal, so far as their weight, size and structure were concerned,



A



B

FIG. 6.—Sections through the testes of the cocks belonging to Case I. *A*, from the pinealectomized cock; *B*, from the control.

with the exception of Case I, where the gland of the pinealectomized animal seemed to contain more numerous eosinophile cells in the anterior lobe of the organ, than those of the control. Also, the thyroids of the pinealectomized chickens were generally a little heavier than those of the controls. Histologically the vesicles were lined with cubical or columnar epithelium cells and were distended and contained much colloid substance, while those of the controls were lined with flattened cells and remained small. With regard to the adrenal gland, in which the medullary and cortical elements were intermixed and formed columnar groups of cells, there was no clear distinction to be observed between the pinealectomized and the control animals, although the former seemed to possess slightly enlarged cell columns. Other endocrine organs, such as the parathyroids, thymus and pancreas, revealed no peculiar condition either macroscopically or microscopically, in the test animals. The same thing can be said regarding the bursa fabricii.

Discussion. With respect to the male chickens, my results coincide with those of Foa and Zoia exactly, but concerning the female chickens the two authors state no change is to be observed as a result of pinealectomy. While Sarteschi reports that the pinealectomized females dislike copulation, Horrax says on the contrary in regard to guinea-pigs: "Pinealectomized females appear to show a tendency to breed earlier than controls of the same age and weight."

Under these circumstances I lay stress on the finding in the case of the pinealectomized female chicken, namely a premature development of the sexual organs. Although the case is only a single one, the finding is so remarkable (see Fig. 5), that there remains little doubt of the fact that the pineal body acts as an inhibitory organ upon the sexual apparatus to young female animals as well as in the males.

Concerning tumors, of the pineal body there are about 90 cases reported, so far as I know; but only 27 of them are cases occurring before puberty. Only 14 of these cases showed the pineal disorder, (Oestreich-Slawyk,[38] Frankl-Hochwart,[17] Ogle,[39] Nagayo,[35] v. d. Bergh,[23] Boehm,[7] Gutzeit,[22] Odermatt,[37] Raymond-Claude,[42] Bailey-Jelliffe,[4] Horrax,[26] Goldzieher,[21] Takeya,[47] Holzhauer[25]); the others revealing no symptoms of sexual prematurity (Schearer,[45] Williamson,[50] Rydinger,[43] Lord,[32] Marburg,[34] Weigert,[49] Falkson,[15] Coats,[8] Gauderer,[19] Zenner,[51] Hoesslin,[24] Laurence,[30] Newmann,[36] Pappenheimer,[41] Garrod,[18] Giebel[20]). The existence of these negative cases, however, does not prove the uninhibitory function of the pineal body in sexual development, for the pineal disorder would appear only when the other endocrine organs could not compensate for the loss of the pineal body.

In this connection it is interesting to refer to a case of hyperpinealism which Prof. Kosaka* kindly permits me to quote.

It concerns a man aged twenty-one years and four months, who died of tubercle of lungs and ribs. In spite of his age he seemed like a boy of only about thirteen years. There were no pubic hairs, the penis remained very small, the testes being only 1.5 cm., in length, 1.0 cm. in breadth and 0.9 cm. in thickness. The development of the bones was very much retarded, so that a part of the skull still retained a membraneous state. As regards the pituitary body, thyroid gland, parathyroids, adrenals and pancreas, nothing particular was observed, only the pineal body showing a relatively strong development, its transverse diameter being 9 mm. and sagittal length 8 mm. Histologically it had a structure resembling that of a baby's pineal body, the poorly cellulated lymph sinus-like portion remaining remarkably well-preserved, and the trabeculæ of the connective tissue scanty. This case indeed affords another proof of the abovementioned statement concerning the function of the pineal body. Nevertheless it appears somewhat strange that the above quoted 12 positive cases, and the case of Kosaka should all belong to the male sex, while no similar cases are known in women, with the exception of 1 reported by Askanazy and Brock.[2]

According to these authors an idiot woman, who died of an epileptiform fit at the age of twenty-three years, had shown a premature development of sexual character. When she was only ten years old the mammæ became considerably enlarged, at the age of eleven the pubic hair appeared, and two years later she experienced menstruation. At autopsy the pineal body was found as a very rudimentary organ, its weight being only 0.04 gm., its length 3 mm. and its breadth 2 mm. The other endocrine organs revealed nothing uncommon except the thyroid gland which suffered from the change seen in Basedow's disease.

Although Askanazy himself is of another opinion, I think this case supports the theory that the pineal body inhibits the premature development of the sexual organs in the female as well as in the male; and I believe firmly that the theory is valid, for my experimental results in the case of the female chicken prove it conclusively.

Summary. 1. Pinealectomized young cocks grow more rapidly than the controls, begin to crow prematurely, and show an earlier development of the combs and testes.

2. Pinealectomized young hens reveal likewise a premature development of the ovary and Fallopian tube.

3. In the pinealectomized chickens the endocrine organs, except

* The report of this case will appear in the festival publication dedicated to Prof. S. Kure.

for the sexual glands, show nothing abnormal, or only a slight difference, as compared with those of the controls.

4. Therefore it appears that the pineal body's chief function is to repress the premature development of the sexual organs in the female as well as in the male.

BIBLIOGRAPHY.

1. Askanazy, M.: Teratom und Chorionepitheliom der Zirbel, Verhandl. d. path. Gesellsch., Jena, 1906; Centralbl. f. allg. Path. u. Path. Anat., 1906, **17**, 872; Chemische Ursachen und morphologische Wirkungen bei Geschwulstkranken, insbesondere ueber sexuelle Fruehreife, Ztschr. f. Krebsforschung, 1910, **9**, 3.

2. Askanazy, M., and Brock, W.: Sexuelle Fruehreife mit einer Idiotin mit Hypoplasie der Zirbel, Virchow's Arch., 1921, **234**, 1.

3. Askanazy, A.: Die Zirbel und ihre Tumoren in ihrem funktionellen Einfluss, Frankf. Ztschr. f. Pathol., 1920, **24**, 58.

4. Bailey, P., and Jelliffe, S. E.: Tumor of the Pineal Body, Arch. Int. Med., 1911, **8**, 851.

5. Berblinger, W.: Die genitale Dystrophie in ihrer Beziehung zu Stoerungen der Hypophysenfunktion, Virchow's Arch., 1920, **228**, 151.

6. Biedl, A.: Innere Sekretion, 1913, 2d ed.

7. Boehm, E.: Zirbeldruesenteratom und genitale Fruehreife, Frankf. Ztschr. f. Path., 1919, **22**, 121.

8. Coats, J.: An Adenoid Sarcoma with Cartilage Originating in the Pineal Gland, Trans. Path. Soc. London, 1887, **28**, 44.

9. von Cyon, E.: Zur Physiologie der Zirbeldruese, Arch. f. d. ges. Physiol., 1903, **98**, 327.

10. Dana, C. L., and Berkley, W. N.: The Function of the Pineal Gland, Med. Record, 1913, **33**, 835.

11. Dandy, W. E.: Extirpation of the Pineal Body, Jour. Exper. Med., 1915, **22**, 132.

12. Dixon, W. E., and Halliburton, W. D.: The Pineal Body, Quart. Jour. Exper. Physiol., 1909, **2**, 283.

13. Edinger, Bau der nervoesen Zentralorgane, 1908, 7th ed.

14. Exner, A., and Bolse, A.: Ueber experimentelle Extirpation der Glandula pinealis, Neurol. Centralbl., 1910, **29**, 754.

15. Falkson: Ein Chondrocystosarcoma in III Ventrikel, Virchow's Arch., 1879, **75**, 550.

16. Foa, C.: Hypertrophie des testicules et de la crête apres l'extirpation de la gland pineale, Arch. ital. de biol., 1914, **61**, 79; Nouvelles récherches sur la fonction de la gland pinéale, Arch. Ital. de biol., 1914, **61**, 79.

17. v. Frankl-Hochwart, L.: Ueber die Diagnose der Zirbeltumoren, Deutsch. Ztschr. f. Nervenheil., 1909, **37**, 455. Ueber den Einfluss der Zirbelstoerung auf die Psyche, Jahrb. f. Psych. u. Neurol., 1914, **35**, 159.

18. Garrod, A. E.: Tumor of Pineal Body, Trans. Path. Soc., London, 1899, **50**, 12.

19. Gauderer, L.: Zur Kasuistik der Zirbeldruesentumoren, Inaug. Dissert., Giessen, 1881.

20. Giebel, W.: Ueber primaere Tumoren der Zirbeldruese, Frankf. Ztschr. f. Pathol., 1921, **25**, 176.

21. Goldzieher, M.: Ueber die Zirbeldruesengeschwulst, Virchow's Arch., 1913, **213**, 353.

22. Gutzeit, R.: Ein Teratom der Zirbeldruese, Inaug. Dissert., Koenigsberg, 1896.

23. Hijmans van den Bergh en A. van Hasselt: Tumor glandulæ pinealis, sive Epiphyseos cerebri, Nederl. Tijdschr. v. Geneesk., 1913, **1**, 19 (quoted in München. med. Wchnschr., 1913, p. 2140).

24. Hoesslin: Tumor der Epiphysis cerebri, München. med. Wchnschr., 1894, p. 292.

25. Holzhauer, R.: Zur Kasuistik der Gehirntumoren in Kindesalter, Inaug. Dissert., Halle, 1909 (quoted by Schueller in Lewandowsky's Handbuch der Neurologie, 1913, **4**, 342).

26. Horrax, G.: Studies on the Pineal Gland: I. Experimental Observations; II. Clinical Observations, Arch. Int. Med., 1916, **17**, 607.

27. Howell, W. H.: The Physiological Effects of Extracts of Pituitary Body, Jour. Exper. Med., 1898, **3**, 245.

28. Jordan, H. E., and Eyster, J. E.: The Physiological Action of Extracts of the Pineal Body, Am. Jour. Physiol., 1911, **29**, 115.

29. Kidd, L. J.: Pineal Experimentation, British Med. Jour., 1910, vol. **24**.

30. Laurence: Tumor of Pineal Body, Trans. Path. Soc. London, 1899, **50**, 18.

31. Loewy, D.: Die Sekretwege der Zirbeldruese, Arbeit. a. d. Wien. neurol. Inst., 1912, **20**, 130.

32. Lord: The Pineal Gland: Its Normal Structure (Some General Remarks on Its Pathology), Trans. Path. Soc. London, 1899, **50**, 18.

33. McCord, C. P.: The Pineal Gland in Relation to Somatic, Sexual and Mental Development, Jour. Am. Med. Assn., 1914, **63**, 232.

34. Marburg, O.: Die Adipositas cerebralis, Wien. med. Wchnschr., 1908; Zur Prage der Adipositas universalis bei Hirntumoren, Wien. med. Wchnschr., 1907; Zur Kenntniss der normalen und pathologischen Histologie der Zirbeldruese, Arbeit a. d. Wien. neurol. Inst., 1909, **17**, 259; Die Klinik der Zirbeldruesenerkrankungen Ergebn. d. inn. Med. u. Kinderh., 1913, **10**, 146; Neue Studien ueber die Zirbeldruese, Arbeit. a. d. Wien. neurol. Inst., 1920, **23**, 1.

35. Nagayo, M.: Zur Pathologie der Zirbeldruese, Neurologia, 1919, **18**, 1 (in Japanese),

36. Newmann, M.: Zur Kenntniss der Zirbeldruesengeschwulste, Monatschr. f. Psych. u. Neurol., 1901, **9**, 337.

37. Odermatt: Zur Diagnostik der Zirbeldruesentumoren, Inaug. Dissert., Zuerich, 1915.

38. Oestreich, R., and Slawyk (Heubner): Riesenwuchs und Zirbeldruesengeschwulst, Virchow's Arch., 1899, **157**, 475.

39. Ogle, C.: Sarcoma of Pineal Body, Trans. Path. Soc. London, 1899, **50**, 4.

40. Ott, I., and Scott, J. C.: A Preliminary Note on the Pineal Gland, Monthly Cyclop. and Med. Bull., 1911, **4**, 540.

41. Pappenheimer, A. M.: Ueber Geschwulste der Corpus pineale, Virchow's Arch., 1910, **200**, 122.

42. Raymond, F., and Claude, H.: Les Tumeurs de la glande pinéale chez l'enfant, Bull. Acad. de Med., Paris, 1910, 3 s., **63**, 265.

43. Rydygier, R.: Erfahrungen ueber die Dekompression und Trepanation, Deutsche Ztschr. f. Chir., 1912, **117**, 360.

44. Sarteschi, U.: Richerche istologische sulla ghiandola pineale, Folia neurobiol., 1910, **4**, 675; Sindrome epifisaria macrogenitosomia præcoce, Pathologica, 1913, **5**, 707.

45. Schearer: Edinburgh Med. Jour., 1875, **21**, 279 (referred to by Bailey and Jelliffe).

46. Studnicka: Die Parietaleorgane, Oppel's Lehrbuch der vergleichenden microskopischen Anatomie der Wirbeltiere, 1906, vol. **5**.

47. Takeya, H.: Die Erkrankungen der Epiphyse, Nissinigaku, 1913, **3**, 319.

48. Uemura, S.: Zur normalen und pathologischen Anatomie der Glandula pinealis des Menschen und einiger naustiere, Frankfurt. Ztschr. f. Pathol., 1917, **20**, 381.

49. Weigert, C.: Zur Lehre von den Tumoren der Hirnanhaenge, Virchow's Arch., 1875, **65**, 212.

50. Williamson, R. T.: Tumor in the Region of the Corpora Quadrigemina, Med. Chron., August, 1910 (referred to in Neurol. Centralbl., 1911, p. 384).

51. Zenner, P.: A Case of the Tumor of the Pineal Gland, The Alienist and Neurologist, 1892, **13**, 470 (referred to in Neurol. Centralbl., 1893, p. 308).

52. Zoia, C.: Demonstration von Tieren denen die Zirbeldruese entfernt wurde, Centralbl. f. all. Path. u. path. Anat., 1914, **25**, 789.

THE RELATION OF ADDISON'S DISEASE TO AMYLOIDOSIS.

By Morton McCutcheon, M.D.

PHILADELPHIA.

[1] (From the McManes Laboratory of Pathology, University of Pennsylvania and the Laboratory of Postmortem Pathology of the Philadelphia General Hospital.)

In spite of the differences of opinion that still prevail as to the essential pathological anatomy of Addison's disease, it is generally agreed that the vast majority of cases are associated with bilateral destructive changes in the adrenal glands. Most frequently, these lesions are tuberculous; next in order come atrophic changes often due to inflammation and hemorrhage; less commonly, bilateral tumors are found. Among the rarer conditions, gummata, thrombosis, and amyloid have been described.

Amyloid infiltration of the adrenals is a fairly common finding in individuals who have shown no evidence of Addison's disease. Such a condition is not infrequently met with in our autopsies in cases of widespread amyloidosis. The amyloid is present chiefly in the cortex, being deposited between the capillary walls and the parenchymatous cells. The latter undergo atrophy, presumably from pressure and from diminution of the blood supply. In the medulla, amyloid is present as a rule only in small amounts and about the bloodvessels.

But the association of amyloidosis and Addison's disease is an excessively rare one. Indeed only 2 cases have been found in the literature.[1] [2] It should be instructive, therefore, to consider the relation of these two conditions.

The rarity with which amyloidosis produces Addison's disease may be due to the fact that the amyloid lies mostly in the cortex, while the medulla escapes. This explanation would be in harmony with the views of Wiesel, who believed that Addison's disease is always dependent upon lesions of the chromaffin system, whether within the medulla or elsewhere in the body.[4] Von Hansemann[4] and Karakascheff,[5] however, reported cases of clinically typical Addison's disease in which the cortex was severely involved while the medulla remained intact. To this, Wiesel objected that these authors had not investigated the extra-adrenal chromaffin-tissue, changes which might have produced the symptoms. This objection is hard to dispose of conclusively, but it must be recalled that in the human adult the adrenals contain the bulk of the chromaffin-tissue; and if this be preserved, it is surprising that lesions of smaller chromaffin collections should suffice to determine the appearance of symptoms.

Recently, Fahr and Reiche[6] have reported 5 more cases of Addison's disease, with cortical lesions and preserved medulla.

They concur in what is perhaps the most satisfactory opinion, that destruction of either part of the glands is likely to be followed after a shorter or longer interval by the appearance of Addison's disease. It seems probable that products of protein splitting, possibly toxic, are taken up by the adrenal cortex and worked over there, and that from this material the medulla then forms adrenalin. Interruption of this process at either stage might, then, lead to adrenal insufficiency.

If, then, the cortical position of amyloid is inadequate to account for the non-appearance of Addison's disease, we must look for another explanation. This is probably to be found in the fact that in amyloidosis there does not occur complete destruction of the cortical cells, but merely an atrophy and loss of some of them. The remaining cells are presumably capable in most cases of carrying on their necessary function. But in the case herewith reported, either due to excessive injury of the cortex, or to other unrecognized factors, the function of the cortex would seem to have broken down, and the characteristic symptoms followed.

REPORT OF CASE.—*History.*—R. S., adult white female, aged fifty-three years, was admitted to the Philadelphia General Hospital complaining of weakness and swelling of legs and feet.

She stated that she had been well until one year before admission, when she noticed muscular weakness, with some loss of weight. This was followed by marked swelling of both upper and lower extremities. About four weeks before admission epileptiform convulsions began to occur, during which the patient was unconscious. There was occasional vomiting. About this time, she noticed that the color of her skin was altered.

The previous medical history was practically negative.

Physical examination showed a very ill woman with bronzed skin, and dark patches on the mucous membrane of the mouth. She was edematous over the entire body.

In the abdomen a mass was palpated in the region of the cecum. The reflexes were normal. The blood-pressure was 95 systolic, 45 diastolic. On two subsequent examinations the systolic pressure was 95, diastolic 55 and 50.

Laboratory Examinations. The urine showed a trace to a heavy cloud of albumin, a specific gravity of 1010 to 1018, a few hyaline casts, and variable numbers of leukocytes. Blood urea-nitrogen was 20 mg., uric acid 6.6 mg., chlorides 570 mg. Blood counts gave 3,960,000 and 3,270,000 red cells, hemoglobin 50 per cent, leukocytes 9450 and 6000, with 53 per cent polymorphonuclears. Blood and spinal fluid Wassermann were negative.

Course. During her stay of three months in the hospital, the patient had a number of epileptiform convulsions, which could be controlled fairly well by sedatives. She grew gradually weaker, became semistuporous during the last week, and died.

Autopsy. At autopsy the chief findings were as follows: There was a diffuse bronzing of the skin, most marked over the abdomen and breasts, where the pigmentation was nearly black. The lower pole of the right kidney was occupied by a yellow tumor mass, measuring 10 x 10 x 9 cm. No metastasis of the tumor was found (but the brain was not examined). The adrenals were of normal size and shape, but of increased consistency. The cortex was pale yellow to gray. The amyloid reaction with Lugol's solution was positive in the pulmonary artery, the walls of the cardiac chambers except the left ventricle, the aorta, spleen, liver, and left kidney. The adrenals gave a faintly positive reaction with the iodine solution.

Histological examination of both adrenals showed a deposition in the cortex of a glassy homogenous material, occurring in streaks, which lay in the transverse axis of the gland. This substance gave the color-reaction for amyloid with iodine, methyl-violet, and cresyl echt violet. It was so plentiful in the zona fascicularis and zona reticularis that the adrenal cells were present only here and there, scattered through the hyaline material. Nuclei were in some cases well preserved, in others, pyknotic. The cytoplasm was indistinct and the cell outline indefinite. Here and there could be seen the remains of columns of adrenal cells, which had the usual vacuolated appearance. The zona glomerulosa was much less involved than the deeper layers.

The medulla was scanty but well preserved, the cells staining normally. Amyloid was scanty, being chiefly confined to the walls of the bloodvessels, though extravascular collections of the material were seen in some places.

A small collection of ganglion-cells was found outside the adrenal substance. Many of the cells had poorly staining nuclei and some of the cell-bodies were ragged in outline.

Section of the kidney tumor showed a typical hypernephroma of the Grawitz type.

Although amyloidosis is usually the result of chronic suppurating conditions, yet it is not very infrequently found in individuals with malignant tumors, such as hypernephroma. That the tumor was responsible for the amyloidosis in this case cannot be doubted, since no tuberculous or suppurative lesions were found.

Summary. 1. A case of Addison's disease is reported, associated with widespread amyloidosis, which involved the cortex of both adrenals.

2. The amyloidosis apparently resulted from a large hypernephroma.

3. It is held likely that the rarity with which amyloid disease produces the Addison syndrome is not dependent on the preservation of the adrenal medulla, but rather on the fact that the cortex is not completely destroyed by the infiltration, many cell-groups escaping.

4. In the present instance, the destruction of cortex seems to have been severe enough to determine the appearance of Addison's disease.

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BIBLIOGRAPHY.

1. Bittorf: Deutsch. Arch. f. klin. Med., 1910, **100**, 116.
2. Schutz: Cleveland Med. Jour., 1912, **11**, 40.
3. Wiesel: Virchows Arch., 1904, **176**, 103; Ztschr. f. Heilkunde, 1903, **24**, 257.
4. v. Hansemann: Berl. klin. Wchnschr., 1896, **33**, 296.
5. Karakascheff: Ziegler's Beiträge, 1904, **36**, 401, and 1906, **39**, 373.
6. Fahr and Reiche: Frankfürter Ztschr. f. Path., 1919, **22**, 231.

LYMPHATIC OBSTRUCTION: NON-PARASITIC ELEPHANTIASIS.

By L. T. Gager, M.D.,
NEW YORK.

(Instructor in Medicine, Cornell University Medical College. From the Cornell Clinic.)

Under the names of "chronic trophedema,"[1] "œdeme dystrophique,"[2] "elephantoid edema"[3] and "non-parasitic elephantiasis"[4] has been described an edema occurring in non-tropical climates which is characterized by a slow, insidious onset and a chronic, painless non-inflammatory course. The edema is commonly white and hard and free from tenderness on pressure. The lower extremities are most often involved and the subcutaneous tissues and to a lesser extent the skin are alone affected. Sensory changes are very rare. The general health is unimpaired, the common systemic diseases associated with edema are absent and the patient's chief complaint is of the weight or size or unsightliness of the parts in which the chronic enlargement exists.

Except for the lack of a hereditary or familial character, the diseases in this category present precisely the clinical picture described by Milroy,[5] Meige,[1] Rolleston[7] and Hope and French,[8] and variously interpreted as due to trophic changes or vascular neurosis.

In the past year we have had the opportunity of studying 5 cases of chronic edema of the sporadic type, all quite lacking in history of inflammation, particularly of erysipelas or other skin affections. All of these patients were women who gave, in every case, a history of very gradual onset and exhibited varying degrees of persistent swelling of a duration of from nine months to over thirty years.

CASE I.—G. C., aged twenty-two years, female, single, Jewish, a saleswoman, was admitted to the Cornell Clinic on November 3, 1921, with swelling of both legs of six years' duration.

Her family was free from similar disease. She was born in New York City, and in her first decade had had measles, pneumonia and whooping-cough. In 1917, an acutely inflamed appendix was removed at the New York Hospital. No note of increased size of the legs was made at that time. The patient began to menstruate at fifteen years and her periods have been normal. She has had chronic constipation since childhood.

At sixteen she first noticed swelling in both legs, and it occurred "all at once," from ankles to hips on both sides. There was no pain, no redness nor any other evidence of inflammation. She went to many physicians and received many diagnoses, but the enlargement slowly progressed. She has remained at work constantly.

Physical examination discloses a well-nourished girl, of good development and color. Her weight is 120 pounds. The upper extremities and the shoulder and pelvic girdles are normal in contour and without fat deposition. The heart and lungs are clear and all the findings are essentially normal, except for the lower extremities, which are twice the normal size and approximately equal. The skin remains fairly soft and is white. There is no pitting on pressure. The subcutaneous tissues are evidently thickened. There is no tenderness. The resistance suggests fatty overgrowth, but the remainder of the body is normal and there is no evidence of endocrine disturbance, particularly of myxedema or hypothyroidism. There is no enlargement of the inguinal nodes, and no evidence, in the form of thickening, of thrombosis of the femoral vein. The swelling does not involve the labia or abdominal wall.

The roentgen-ray plate showed bony and muscular outlines of normal size, while the subcutaneous tissues varied from 1 to $1\frac{3}{4}$ inches in thickness. The sella was negative. In the endocrine clinic no evidence of incretory gland disturbance was found; a chronic pelvic inflammatory condition related to the appendix was considered as a possible factor, causing lymphatic blockage, and the diagnosis of elephantiasis was accepted. The young woman will not consider surgical treatment; recently she has expended a considerable sum on "electricity," without improvement.

CASE II.—A. M., aged fifty-two years, female, married, American, an office manager, came to the clinic on May 15, 1922, because "her limbs were badly swollen and were getting worse."

In her family there was no similar condition. Her past history was one of excellent health. At the age of fourteen years, following a fall, she had a swelling of the left knee, which was placed in

a cast for six months, without improvement. The swelling went on until the entire left leg was involved, first from knee to thigh and then from knee to ankle. The patient was not aware of inflammation at any time and the enlargement has been free from pain. The condition progressed, and at the age of twenty-five years, eleven years after the onset, she was told she had kidney trouble. In 1901, she went through six weeks of typhoid fever without complications. In 1908, at the age of thirty-six years, she first noticed a swelling of the right ankle, and this went on until the enlargement reached the knee, beyond which it has not advanced. The size of her legs is affected by posture; she keeps her feet elevated at night in order to be able to get her shoes on in the morning. The advent of short skirts has accentuated the patient's distress over her large extremities. Her weight has been stationary for five years.

The physical examination shows a well-developed and well-nourished, but not obese, woman of middle age, without abnormal findings except for the marked enlargement of the lower extremities, particularly from knees to ankles. The right calf at its mid-portion measures 19 inches and the left 22 inches in circumference. There is no pitting and no tenderness. The thighs are soft, perhaps slightly larger than normal. The skin over the legs is dry, firm, not to be picked up between the fingers, and very slightly reddened. There are no enlargements of the inguinal nodes. Pelvic examinations have been negative repeatedly and the Wassermann test is negative.

Case III.—J. F., aged twenty-three years, female, single, stenographer, came to the clinic on June 15, 1922, because of swelling of the right leg of nine months' duration. She had been told she had phlebitis.

The family history is negative. The past history includes "St. Vitus' dance" for nine months at the age of fifteen years. She had no tonsillitis or rheumatic fever. Her cardio-respiratory and gastrointestinal history is entirely negative. Her menses began at fourteen years and she "grew up suddenly" in the year following. Her periods occur every twenty-eight days, last five days, with moderate flow and without pain. She was born and has always lived in New Jersey, and her habits are unexceptionable.

The present illness began in September, 1921, when the patient noticed a swelling of the right ankle which was not associated with trauma or pain. The swelling progressed slowly and painlessly, and three months later there was a noticeable enlargement from the ankle to the hip. The patient believes her leg is still getting larger. It varies with posture, decreasing with elevation. At no time has there been tenderness, and no inflammation of the skin has been present. The girl complains of some stiffness in the

right hip. She has gained weight. At the time of the onset of the swelling in the ankle she thinks the right labium was slightly swollen.

The examination discloses a moderately tall and slender girl, of fair development. Her weight is 111 pounds. Her color is good, the pupillary reactions are normal, the tonsils are small, the teeth are excellent and the thyroid is not felt. The heart, lungs and abdomen are without pathological findings. The right leg is swollen from the hip down. There is pitting on pressure over the right tibia. The skin remains soft and is not discolored. There are no varicosities. The inguinal nodes are not enlarged. The deep vessels in the groin are not palpably thickened. The left leg is normal. The comparative measurements are: Mid-thigh: right, 18 inches; left, 15½ inches. Mid-calf: right, 14 inches; left, 12 inches. The knee-jerks are normal. The blood-pressure is 108 systolic and 72 diastolic. There is a very faint trace of albumin in the urine.

The diagnosis of lymphatic blockage was proposed and the question of curative treatment discussed. The patient has never returned for the surgical consultation, as she was directed by friends to a doctor who had just returned from a trip to the Orient and knew that her condition could not be elephantiasis. She has written that she is being treated for a thrombosed vein with elevation of the foot and tablets to "dissolve clot." A recent letter states that she feels better, but the swelling is still present.

Case IV.—R. H., aged fifty-eight years, female, married, German, housewife, was admitted on July 20, 1922, with the complaint of swelling of the legs and backache.

Of the family history, the patient remembered that a sister in Europe had a swelling of the legs but was ignorant of its nature. Her past history was one of robust health. She had born 11 children without miscarriage, "milk-leg" or other complications. The pain in the back was of some years' standing.

The present illness dated from 1920, when swelling of both legs became rather marked. By the time of her second visit, however, she had remembered that she had noticed slight swelling, beginning twenty years previously, at the age of thirty-eight years. She had been treated in Bucharest and other Continental clinics without improvement. She had had no pain or inflammation, and she came to get medical attention only when a friend commented upon the size of her swollen feet.

This patient is an obese woman, weighing 167 pounds. The physical examination is essentially negative. There is no definite localization of the fat and no evidence of endocrinopathy. The thighs give normal measurements, 21 inches in their midportion on each side. From the knees to the ankles there is marked enlarge-

ment of both legs, measuring 15¼ inches at the midpoint of each calf. There is no pitting, no tenderness and little pigmentation. The subcutaneous tissues are thickened. There are slight superficial venous varicosities. No enlargement of the lymph nodes were made out in popliteal or inguinal regions.

The urine and blood-pressure are normal.

CASE V.—N. W., aged twenty-eight years, female, single, Irish, telephone operator, came to the clinic on February 16, 1922, for a cold in the head This was relieved and the patient was not seen until October 30, 1922, when she returned for indigestion, and was sent to the department of medicine for the first time. Her family history was negative. Her past history was free from illness, except for influenza in 1919. Her present illness, "heavy stomach," gas and occasional "cramps," is of a year's duration. She is afraid of cancer. Her physical examination is entirely negative, except for marked enlargement of the legs below the knees. Questions regarding this bring out the facts that the swelling began at the age of fourteen years with the establishment of menstruation. There was slight tenderness of the skin at the beginning, but no inflammation and no fever. The size of the lower legs has always annoyed her and for the past two years has been increasing slightly. The legs are definitely larger at night than in the morning. At the present time the skin is slightly thickened, the subcutaneous tissues more so. There is no pitting at this examination and no tenderness. The blood-pressure is 104 systolic and 62 diastolic. The urine is normal.

The question at once arises whether such conditions as are presented in these patients may be grouped correctly under the heading of elephantiasis, a term which, of course, serves to call to mind the huge pachydermous enlargements associated with filariasis and lymphatic obstruction which give the tropical disease its name. The characteristic features of elephantiasis, strictly speaking, are two in number: Chronic edema and proliferation of the subcutaneous connective tissue secondary to this edema, and the pathological basis for the edema is the blocking of the lymph circulation.

Manson[9] states that "lymph stasis alone does not produce elephantiasis," by which he means a true hypertrophy of the subcutaneous tissue, for which "inflammation in an area of lymphatic congestion is prerequisite." He further states that "simple lymphatic edema in areas which have never become inflamed subsides readily enough on pressure or elevation."

Matas[3] defines elephantiasis at some length as "a progressive histopathological state or condition which is characterized by a chronic inflammatory fibrosis or hypertrophy of the hypocermal

and dermal connective tissue, which is preceded by and associated with lymphatic and venous stasis, and may be caused by any obstruction or mechanical interference with the return flow of the lymphatic and venous currents in the affected parts." Matas also maintains that mechanical obstruction alone is not sufficient to cause this characteristic hypertrophy of the subcutaneous tissues, but that secondary and repeated bacterial invasion, usually streptococcal, is essential. Such secondary infection, he states, is required whether the primary obstruction is due to filariæ, to lymphangitis, to adenitis or to thrombophlebitis; and the tropical incidence of the disease is due not to filariasis chiefly, but to the greater exposure of the unclothed body to traumata, parasites and infections of the skin.

That lymphatic obstruction alone may be the cause of persistent edema that is little or not at all relieved by such measures as elevation, compression and massage is shown by the disappearance of the edema when new channels are provided for lymph flow. Indeed, a brilliant chapter in the physiology of the lymph circulation has been contributed by recent surgery, and it is the possibility of great and permanent relief by an operative procedure attended by very little danger that makes the recognition of this disorder of importance.

In the study of edema of the arm associated with the more chronic forms of mammary carcinoma, either with metastases to the axillary nodes or their excision, Handley[10] was able to exclude venous obstruction as a factor by reason of the absence of edema after excision of the axillary vein or its total compression by cancerous masses. By the use of silkworm gut as a means of replacing the occluded or absent superficial lymphatic channels, he met with notable success in reducing the edema. The same was not true when he and others attempted this means of drainage in the leg. But this work goes to show clearly enough that lymphatic blockage alone causes persistent edema and that the definition of elephantiasis will gain in clearness if venous obstruction as a cause is excluded.

The treatment of chronic edema in the lower extremity was solved by Lanz[11] in a case of elephantiasis of five years' duration. The onset had been slow and painless until the size and weight interfered with the man's work. Elevation of the leg brought no result. Multiple incisions of the fascia lata and fascial strips into the marrow of the femur resulted in permanent relief of the edema. The operation served to confirm the anatomical observations of Sappey[12] and the later studies of Delamère, Poirier and Cuneo,[13] which showed the independence of the superficial and deep lymphatics of the extremities, the deep fascia forming an absolute barrier in contrast with views fairly commonly held of the free anastomosis of the lymphatic vessels. As another means

of replacing lymph channels, Lanz suggested transplantation of the spermatic cord, with its rich lymphatics, to bridge an inguinal barrier. Although this was never knowingly carried out, it is of interest that one of Milroy's series, a male born with edema of the foot, had testicular enlargement at maturity, and an operation for removal of the testicle was followed by permanent disappearance of the edema.

Kondoleon[14] followed with a simplified technic of fascial division and removal and reported a series of successes that have attracted general attention. From his large experience, Kondoleon divides elephantiasis into a milder form manifesting only lymph stasis and the more advanced sclerotic type—the result of connective-tissue proliferation. The causes of lymphatic obstruction in his cases included acute inflammations of the foot, tuberculosis of the knee-joint, total extirpation of the inguinal nodes and traumata. There was absence of any injury or inflammation in the case of a woman, aged thirty years, with involvement of the entire right leg for ten years. The formation of new lymph channels after operation was indicated in a patient with edema of fourteen years' duration by the recurrence of the edema shortly after operation and its subsequent spontaneous subsidence. Kondoleon found the lymph stasis occurring chiefly at the fascia lata in his cases; the superficial layers of the fascia were thickened while the surface toward the muscle was always normal. The skin in these patients varied, but was in general moderately thickened, pale, hard and not to be picked up in folds. In one patient there was free exudation of a serous yellow fluid.

Summarizing these cases that have come to operation and others reported by Matas,[3] Sistrunk[15] and other surgeons in this country, conclusive evidence is presented of the role of lymphatic blockage in the production of persistent edema and subcutaneous thickening such as form the chief characteristics of the cases in our series. Following the grouping adopted by Bradbury,[4] the cases that fail to give a history or signs of inflammation may be satisfactorily classified as non-parasitic elephantiasis in contrast with elephantiasis arabum of filarial origin and elephantiasis nostras following erysipelas or frank bacterial infection. When the dystrophic edemas and trophedemas of the French and English writers are considered in the light of the newer lymphatic knowledge, one is inclined, in the absence of definite neurological findings, to include these forms, as well as various isolated cases of unsatisfactorily explained chronic edema (myxedema fruste, Hertoghe, and segmentary edema, Debove) under the heading elephantiasis.

The differential diagnosis of elephantiasis, or edema due to lymphatic obstruction, is of considerable interest. All of the many causes of edema are to be passed in review, and most of them, such as cardiac decompensation, renal disease, the blood

dyscrasias and nutritional disturbances can be promptly excluded. The edema that follows phlebitis is rarely of such long standing, or so firm in consistency, and here also there is rarely lacking a definite history of localized inflammation usually occurring after some primary disease. The question of obesity, either general and due ordinarily to sedentary life, and too much food, or localized and due to endocrine disturbances, notably hypothyroidism and hypopituitarism,[16 17] must be considered; but this can usually be decided from the history and the physical characteristics of the enlargement. Myxedema also is differentiated by its characteristic signs and history. The acute swellings, of the nature of angioneurotic edema, do not, of course, enter into consideration. There is a small group of edemas associated with disease of the central nervous system, with or without muscular paralyses, and probably due to vasomotor changes, as in the classical Ranvier section of the sciatic nerve after the femoral vein had been ligated. In another small group, called by Krehl[18] "essential" edema, no explanation in the way of an external factor causing edema could be found.

In the cases of this series the edema might be regarded as "essential" were it not for what has been definitely shown of lymphatic obstruction and its relief. One can only speculate why all of these cases occurred in women, and in 3 of them at the age of puberty. One of Sistrunk's cases was a girl of seventeen years, whose right leg began to swell at the age of twelve without apparent cause, though she had infected tonsils. Benedict's[6] two cases were women of middle age, with onset of unknown origin. Only one man in this clinic has been seen with edema of more than a few weeks' duration, and that in a patient with recent pneumonia and typical femoral phlebitis. In these women, then, in the absence of anatomical evidence of obstruction such as enlarged nodes or lymphangiectases and clinical manifestations, past or present, of infection, one must be content with suggesting chronic lymphadenitis, chronic lymphangitis, traumata and compression as the result of circulatory or inflammatory changes within the pelvis as etiological possibilities.

The physiology of edema has been adequately discussed by numerous writers,[19 20] and the basic fact is that when lymph production exceeds lymph absorption edema results. The production of lymph under the wide range of pathological conditions associated with edema has given rise to an equal diversity of theories recording its formation. During life only the great lymphatic trunks can be distinguished, and the study of the system post mortem has great technical difficulties. Consequently, the obscurity in which the lymphatics have remained in contrast with the other two great divisions of the circulatory system. It is necessary to remember, as Sabin[21] has pointed out from her beautiful embryological studies, that the lymphatic problem is a fundamental part of the vascular problem.

Summary. Five cases of persistent edema associated with thickening of the subcutaneous tissues and minor skin changes are reported. The edema is hard, white and not accompanied by sensory changes. The absence of frank inflammation at the onset or during the course of the disease is striking. The general similarity of these cases to what has been described as trophedema and dystrophic edema is pointed out. Except for the lack of a hereditary or familial character this type of edema bears a remarkable resemblance to the disease first described by Milroy.

Edema as found in these patients, in the light of recent knowledge, appears to be due to obstruction of the lymphatic channels and may be classified as elephantiasis of a non-parasitic type. Surgical treatment of these cases alone gives a good prognosis as regards their cure.

REFERENCES.

1. Meige, H.: Nouv. iconog. de la Salpêtrière, Paris, 1899, **12**, 453; 1901, **14**, 465.
2. Vigouroux: Nouv. iconog. de la Salpêtrière, Paris, 1899, **12**, 481.
3. Matas, R.: Am. Jour. Trop. Dis. and Prev. Med., Baltimore, 1913, **1**, 1.
4. Bradbury, S.: Nelson Loose Leaf System, New York, vol. **4**, p. 626.
5. Milroy, W. F.: New York Med. Jour., 1892, **56**, 505.
6. Benedict, A. L.: New York Med. Jour., 1915, **102**, 1028.
7. Rolleston, H. D.: Lancet, London, 1902, **2**, 805.
8. Hope and French: Guy's Hosp. Repts., 1908.
9. Manson, P.: Tropical Diseases, New York, 7th ed., 1921.
10. Handley, W. S.: British Med. Jour., London, 1910, **1**, 853, 922.
11. Lanz, W.: Zentralbl. f. Chir., Leipzig, 1911, **38**, 3, 153.
12. Sappey: Anatomie, Physiologie, Pathologie des vaisseaux lymphatiques, Paris, 1874.
13. Delamère, Poirier and Cuneo: The Lymphatics (trans. by Leaf), Chicago, 1904.
14. Kondoleon, Emm: München. med. Wchnschr., 1912, **59**, 525, 2726; Zentralbl. f. Chir., Leipzig, 1912, **39**, 1022.
15. Sistrunk, W. E.: Jour. Am. Med. Assn., 1918, **71**, 800.
16. Cushing, H.: The Pituitary Body and its Disorders, 1912.
17. Engelback, W.: Med. Chir., N. A., 1922, **6**, 1.
18. Krehl, L.: Pathologische Physiologie, Leipzig, 1914, 8th ed.
19. Starling, E.: Principles of Human Physiol., Philadelphia, 1920, 3d ed.
20. Wells, H. G.: Chemical Pathology, Philadelphia, 1920, 4th ed.
21. Sabin, F. R.: Johns Hopkins Hosp. Repts., 1917, **17**, 347.

AN ANATOMICAL BASIS FOR FUNCTIONAL MURMURS.

By J. Epstein, M.D.,

ATTENDING IN PEDIATRICS, VANDERBILT CLINIC; CHIEF OF PEDIATRICS AND CARDIAC CLINICS, BETH ISRAEL HOSPITAL, NEW YORK.

The interpretation of cardiac murmurs has always been of great interest and uncertainty. Errors in the diagnosis of murmurs are not infrequent and their clinical deductions are not always borne out by the pathological findings. All murmurs indicate

some abnormality in the cardiovascular structure. A murmur is an echo of a vibrating heart or bloodvessel, caused by the blood stream being compelled to detour its course, traverse a rough surface, or strike against an inefficient or relaxed valve. While a murmur does not always mean a sick heart and the absence of a murmur does not prove a sound heart, yet a murmuring heart shows that there is something out of order. A murmur may be consistent with perfect health, or it may presage a gradual cardiac decadence.

In the routine examination of patients one frequently finds a cardiac murmur without any other evidence of heart disease to which the name of accidental, inorganic, hemic, or functional murmur has been applied. Accidental murmur is a meaningless term and should be discarded. Inorganic murmur is an ill-adapted term, as all changes in the heart are of a living character. Hemic murmur suggests that the murmur is caused by anemia. But not all anemic patients have murmurs. I have examined a number of anemic patients with a view to finding a cardiac murmur and have found a hemic murmur in a limited number of cases only and without any definite relation to the severity of the anemia. The anemia is probably a contributing factor and the real cause for the murmur may be found in some anomaly of the cardiac muscle tissue. Functional murmur has no generic significance unless it implies a definite cardiac function which, when disturbed, gives rise to a murmur. It is only when a murmur is caused by some abnormality in one of the physiological cardiac functions that the term functional murmur becomes intelligible.

Functional disorders whether applied to cardiology, neurology, or to any other branch of medicine lacks clearness of meaning. As there is no living structure without function so there is no function without structure and disturbances of function must necessarily imply disturbances of structure whether they are perceptible or not. And functional murmurs must therefore have an anatomical substratum.

The heart in its normal action is governed by the following five physiological functions: Stimulus production, excitability, conductivity, contractility, and tonicity. In concord with the skeletal muscle, the cardiac muscle is always in a state of tonus. The heart never relaxes entirely during its restful period or diastole. It always maintains a certain amount of tonic contraction.

Any local or general disorder which will lower the physiological function of tonicity will give rise to a condition of atonia cordis or myatonia cordis. The heart is then unable to contract forcibly during systole and is unduly relaxed and dilated during diastole. There may be a certain amount of residual blood in the ventricles after cardiac contraction. With each impact of blood during systole the relaxed heart and its valves vibrate and there may be

a slight regurgitation. This cardiac vibration gives rise to a soft blowing systolic murmur which has received a variety of names. But since the murmur is the result of some alteration in a physiological cardiac function, namely, tonicity, the term functional murmur has the nearest claim.

Whether the so-called functional murmur with its possible slight regurgitation serves some useful purpose in the mechanism of the heart and in that sense it is purely physiological, or it borders on the realm of the pathological, is still a mooted point. Patients are frequently seen who for many years have this blowing systolic murmur with no apparent impairment of health. In others with the same kind of murmur there is evidence of a general muscular weakness, the blood-pressure is low, and there is a drooping of the heart and abdominal organs.

In all cases of functional murmurs there is evidently no anatomical damage or circulatory inefficiency, but a condition of a lower grade of cardiac tonus. This may be a congenital peculiarity of the cardiac musculature, as the soft blowing systolic murmur is quite frequently heard in infants and young children and persists to adult life. The presence of this murmur in early life and its persistence for many years suggests a congenital origin. The acquired functional murmurs which are heard in older children and adults may be caused by febrile conditions, cardiac fatigue, anemia, malnutrition, improper cardiac innervation, and by hypoadrenia, when acting on a heart of poor muscular tonicity. This murmur usually disappears with the removal of the cause which lowered the muscle strength.

The murmur may be heard in any of the valvular regions but especially in the mitral and pulmonic areas. The diagnosis of a functional murmur is occasionally difficult. Endocardial and myocardial murmurs, during good compensation, and certain cardiopulmonary murmurs, may at times, be indistinguishable from functional murmurs. But if to the objective sign of a soft blowing systolic murmur, limited in its extent, in a heart of normal dimensions, there will be added the health of the patient and his previous history, the diagnosis will become comparatively easy. It is the patient behind the murmur that makes the diagnosis in doubtful cases.

As tonicity is one of the primary physiological functions of all muscle tissue and is an inherent quality of cardiac muscle, a myogenic property, a lowering of muscle tone must effect the final anatomical unit, the muscle fiber. Since the indefinite group of murmurs which are known as accidental, inorganic, hemic, or functional may be caused by a lack of cardiac tonus, the term myatonic murmur, to take the place of the miscellaneous names, would perhaps be more appropriate. It would at once suggest a physiological dysfunction and an anatomical basis.

Summary. In brief, a murmur is frequently heard in children and young adults which cannot be traced to embryological cardiac malformation, endocardial valvular deformity, or to myocardial disease. Because of its uncertain etiology it has received many names which are used carelessly and interchangeably. The uncertainty in the origin of this murmur has also led to its being either totally disregarded or too seriously evaluated. It is therefore of considerable importance for theoretical as well as for practical reasons to put this murmur on a certain scientific basis.

Since nothing constant or definite has been found in the heart or in its circulating fluid to account for this murmur, it is evidently not caused by pathological changes in the cardiac structure, but by physiological disorders in some function of the cardiac muscle tissue; that is, by physiological dysfunction in the cardiac anatomy. Atonia cordis, or a deficiency in the physiological function of cardiac tonus may be the basis for this murmur. Cardiac hypotonia may be of congenital origin or caused by malnutrition, anemia, cardiac fatigue, hypoadrenia, improper nerve control, or by febrile diseases. An atonic, relaxed heart will be unduly stretched by the sudden intraventricular impact during systole and give rise to abnormal vibratory movements and to a soft systolic murmur. The murmur will appear or disappear with the underlying condition that lowered the cardiac muscle strength. This is probably the origin of the oft-heard systolic murmur on which was bestowed a variety of names. But since the origin may be traced to a defective cardiomuscular tonicity, the condition may properly be called myatonia cordis, and the murmur itself myatonic murmur. The diagnosis rests on the fact that the murmur is an isolated objective sign without subjective symptoms and without a history of a previous heart-damaging illness. The prognosis is generally good, but there is always an element of uncertainty, because a perfectly normal heart does not murmur. The treatment is that of the patient and not of the heart.

PAROXYSMAL VENTRICULAR TACHYCARDIA:

Report of a Case of Unusual Type.

By David Felberbaum, M.D.

NEW YORK, N. Y.

(From the Medical Division of the Montefiore Hospital for Chronic Diseases.)

Paroxysmal tachycardia of ventricular origin is sufficiently uncommon to warrant the reporting of isolated cases. It can only be definitely differentiated from that of auricular origin by means of the electrocardiograph. It is the result of a rapid and regular succession of ventricular ectopic beats.

The relative frequency of its occurrence may be judged by the following statistics. Among 2400 soldiers invalided during the recent war for D.A.H. and V.D.H., Hume found 6 cases of paroxysmal tachycardia, which he described as of ventricular origin. In 3 of these cases electrocardiograms were obtained, 2 of which were undoubtedly cases of this condition. Willius gives the occurrence as .04 per cent of all abnormal electrocardiograms encountered at the Mayo Clinic. Hart records 1 case in a series of 17 cases of paroxysmal tachycardias, while Vaughan found 2 among 18.

The incidence of this type of arrythmia is definitely less frequent than the foregoing statistics would indicate. In a recent review of this subject made by Robinson and Hermann of all the cases of paroxysmal tachycardia of ventricular origin which were previously published with electrocardiograms they have come to a similar conclusion. Of 16 cases so recorded only 6 were acceptable by them as undoubted cases of paroxysmal tachycardia of ventricular origin; while 6 other cases were considered as probable.

This is explained by the fact that isolated auricular extrasystoles may at times be followed by varying degrees of blocking in the ventricular conduction system, as originally pointed out by Hewlet. Furthermore, electrocardiographic studies have shown that this disturbance may be limited to either branch of His's bundle and will be recognized as aberration of the ventricular complexes. In high grade tachycardia the conduction through the ventricles is more likely to become defective and aberrations of the ventricular complexes appear in the electrocardiograms. In a prolonged paroxysm it is manifestly impossible, because the aberrations resemble closely ventricular extrasystoles, to distinguish an auricular from a ventricular paroxysm of tachycardia, unless distinct evidences of the auricular activity are visible at a slower and independent rate. The most certain way of unravelling the tachycardia is by careful analysis of the onset or offset of an attack, especially the type of extrasystoles occurring during these transitional stages. If these are typically ventricular in form and identical with those occurring during the spell, we can be reasonably certain that the site of impulse formation during the abnormal rhythm is in the ventricles. Unfortunately it is not always possible to record these transitions and many cases must be left in doubt. In cases of established auricular fibrillation such difficulties as a rule do not arise, the tachycardia, if paroxysmal is unquestionably ventricular in origin.

The following tabulation shows at a glance the essential clinical and pathological data of all the cases reported in the literature with graphic records.*

* Since this article was accepted for publication another case appeared in the literature. This was an undoubted case of ventricular tachycardia, the site of origin of the abnormal rhythm was in the right ventricle, and caused retrograde contraction of the auricles. The attacks were successfully controlled by quinidine.

EDITORS' NOTE.—Four cases have recently been reported by C. C. Wolferth and T. M. McMillan (*Arch. Int. Med.*, 1923, **31**, 184) and one by Gallivardin (*Arch. d. mal. du cœur*, 1922, **15**, 298.)

Authors.	Undoubted cases.		Probable cases.		Doubtful cases.		Site of ectopic foci.	Autopsy findings.	Remarks
	Sex.	Age.	Sex.	Age.	Sex.	Age.			
Lewis	M.	..	..	..	..	..	Right ventricle	.....	Independent auricular activity visible.
	M.	..	..	..	..	..	Left ventricle	.....	A-V block.
Hart	M.	49	..	..	..	..	Right ventricle	.....	Independent auricular activity visible, probably retrograded from ventricular. Syphilis? Improved.
Cohn and Fraser	..	..	M.	43	..	..	Right ventricle	.....	Left vagus pressure controlled attack.
Butterfield and Hunt	M.	45	..	..	..	..	Left ventricle	Sclerosis of mitral and aortic valves. Extensive degeneration and fibrosis of left ventricle and septum	
Willius	M.	62	..	..	..	..	Right ventricle	In one case autopsy showed atheroma of left coronary artery	Probably auricular tachycardia.
	..	..	..	..	F.	21	.....		
	M.	42	..	..	..	..	Right ventricle		
	..	..	F.	44	..	..	Left ventricle?		
	..	..	M.	38	..	..	Left ventricle?		
Vaughan	M.	21	..	..	..	..	Left ventricle	.....	C. C. V. D. mitral and aortic insuff. hypertrophy.
	M.	50	..	..	..	..	Left ventricle	.....	Auricular tachycardia followed by ventricular tachycardia.
Hume	..	..	..	..	M.	20	.....	.....	Probably auricular tachycardia.
	M.	..	..	..	..	..	Right ventricle	.....	All in soldiers with no evidences of cardiac disease.
	M.	..	..	..	..	..	Left ventricle		
Lea	..	..	M.	55	..	..	.....	Aorta and coronaries markedly atheromatous	Auricular fibrillation with high degree of A-V block. Attack of ventricular tachycardia studied by polygraph record.
Gallavardin	M.	59	..	..	..	..	Left ventricle	Extensive atheroma of aorta. Valvular and myocardial sclerosis	Auricular activity visible. Controlled by vagus pressure.
	..	..	M.	63	..	..	Left ventricle	Syphilitic aortitis and coronary plaques in left ventricle	At first auricular flutter terminated by ventricular tachycardia.
Robinson and Herrmann	M.	59	..	..	..	..	Left ventricle	.....	Auricular fibrillation.
	M.	53	..	..	..	..	Left ventricle	Syphilitic occlusion of ant. descending branch of left coronary	Auricular complexes visible.
	M.	58	..	..	..	..	Left ventricle	.....	Auricular complexes? Chronic nephritis, exitus.
	F.	53	..	..	..	..	Left ventricle	.....	Dropped dead six months after discharge.
	M.	49	..	..	..	..	Right ventricle	.....	Lues, improved under treatment; auricular complex visible.
Schwensen	F.	61	..	..	..	..	Rt. and lf. alt.	Old endocard. of mitral valve. Hypertrophy and dilatation	Rheumatic history, auricular fibrillation.
Writer's case	F.	54	..	..	..	..	Rt. and lf. alt.	.....	Chronic nephritis, arteriosclerosis, myocarditis, auricular fibrillation.
Total	18 M–15 F– 3		5 M–4 F–1		2 M–1 F–1		Left ventricle 11 Right ventricle 7 Left doubtful 2 Bilateral 2		

The condition is very much more frequent in males, and in all the cases except those reported by Hume, the patients presented evident symptoms of grave cardiac involvement. The death-rate has been extremely high. The frequent occurrence of coronary disease in this condition is to be noted, and is significant in view of the experimental production in animals of ventricular tachycardia by ligation of the coronary arteries. Syphilis has been a factor in a few cases. The possibility of digitalis producing paroxysmal tachycardia is discussed by Hart, Vaughan and Schwensen. It is known that experimentally paroxysms of ventricular tachycardia can be produced by chloroform, digitalis and strophanthin. In hearts that are badly decompensated, showing high degree of myocardial degeneration with extreme dilatation and in which digitalis medication is pushed, toxic effects are easily induced, such as coupling and even ventricular tachycardia (D. Danielopolu).

In all the cases so far published with electrocardiograms, the paroxysm was produced in a single focus arising in either ventricle, most frequently the left. The case which we observed at the Montefiore Hospital was unique and only recently Schwensen reported a similar case. In both the paroxysms were the results of alternately recurring right and left ventricular extrasystoles.

Case Report.—H. G., female, aged fifty-four years, housewife, was admitted to the Montefiore Hospital December 30, 1920, complaining of the typical train of symptoms due to cardiac decompensation; namely general weakness, attacks of palpitation, dyspnea, orthopnea, swelling of the feet, ascitis, insomnia and frequency of urination. The family history was essentially negative.

Past History. She had had no serious illness until the onset of the present trouble. Menses appeared at twelve years, menapause at fifty years. She was married at twenty years, had 10 pregnancies, with 7 living children. She had 1 miscarriage, 2½ months, 10 years previously. Deliveries and puerperia were normal. There was no venereal history. She had always worked hard, had insufficient sleep and kept irregular hours. Was moderate in all other respects.

Present Illness. About six years previous to admission, after a hard day's work, patient had a sudden attack of faintness. Following this she was bedridden for six weeks. She had great difficulty in using her left arm and leg. The left eye remained open and her mouth was drawn toward the left. She had difficulty in speaking and chewing. At the end of about six weeks the symptoms cleared up. The following year the patient was able to go about her usual duties although she did not feel as strong as formerly. Three years ago she had a sudden attack of dyspnea, with cough and weakness, but no edema. A few weeks of rest cleared up the symptoms, the patient again resumed her work and since then

has had several similar attacks, feeling always weaker after each one. In August, 1920, she had a final attack and this time the dyspnea, cough and weakness were accompanied by palpitation, edema and ascites. A few weeks in one of the hospitals of the city resulted in the clearing up of the symptoms, except the weakness and shortness of breath. Two weeks before her entrance into Montefiore Hospital, the ascites returned and she was barely able to be up and about.

Physical Examination. The patient appeared much older than her age of fifty-four years. She was of medium stature, poor nutrition and the mucous membranes were slightly cyanotic. The nose and throat were essentially negative but all the teeth were missing. The pupils were slightly irregular, the right one being smaller and reacted sluggishly to light. There was a fulness and pulsation in the vessels of the neck, both venous and arterial.

The *thorax* was symmetrical and of fair size. The lungs revealed some dulness at both bases, where there were a few moist rales. The cardiac impulse was poorly discernible, diffused and the maximum impulse was felt in the sixth space in the anterior axillary line. No thrills were palpable. The transverse diameters were much enlarged. The heart was fibrillating, rapid and a systolic murmur was audible, best heard over the apex and transmitted into the axilla. The pulse deficit varied between 10 and 20 beats. The radials were thickened and the blood-pressure was 175/75.

The *abdomen* was pendulous; diastasis of the recti was marked. The dependent portions were edematous. The liver's sharp edge was palpable about four fingers below the costal margin, not pulsating but tender. The spleen and kidney were not felt and there was no ascites. There was slight edema of the lower limbs, and cyanosis of the nail beds. Neurological examination was essentially negative.

The urine was acid, the specific gravity varied from 1010 to 1025. There was always a trace of albumen but no sugar. During the last week blood cells were present, hyalin and a few granular casts were constantly seen.

The Wassermann reaction was negative.

The diagnosis was arteriosclerosis, chronic nephritis, endomyocardial disease with mitral insufficiency, auricular fibrillation and hypertension. Terminal paroxysmal ventricular tachycardia.

The first electrocardiograms were taken on January 7, 1921, and showed a typical auricular fibrillation of a fine character, with a left ventricular predominance. The rate of the heart varied between 94 and 150. The rhythm was completely irregular, but no premature beats occurred at this time. Fig. 1.

Course. During the first two months of her stay in the hospital, the patient improved considerably under medication with digitalis and theobromin sodium salicylate. The heart-rate became slower

and the dypsnea and other subjective symptoms diminished in severity. During the month of February, she developed an acute psychosis, lasting about two weeks and characterized by sleeplessness, irritability, disorientation and noisy delirium. With this her compensation suffered greatly, the pulse deficit increased and the edema of the limbs reappeared. There was an accumulation of fluid in the left pleural cavity, but not sufficient for aspiration. Her mental condition gradually cleared up, following which heavy

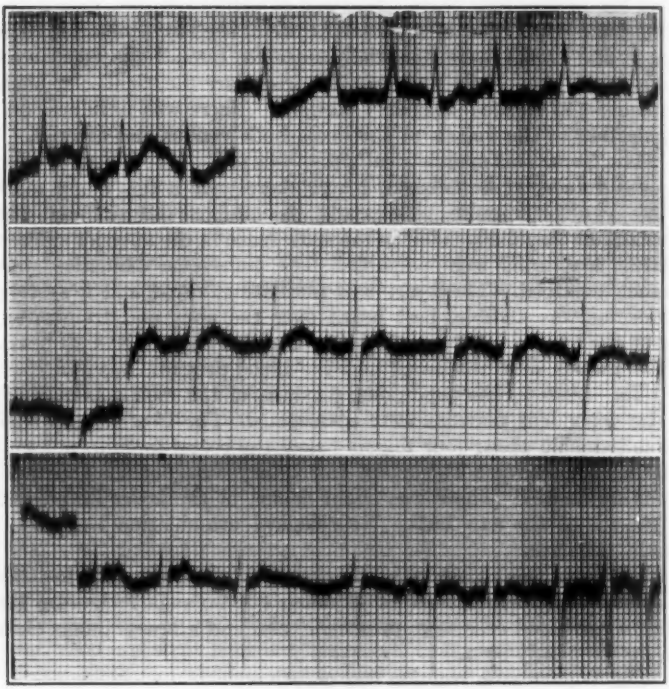


FIG. 1.—Record obtained January 7, 1921. Auricular fibrillation. Left ventricular preponderance.

doses of digitalis, theobromin sodium salicylate and a Carrel diet were instituted for the progressive edema. In spite of this the pulse remained rapid, irregular and a large pulse deficit was constant. The urine became very scanty and almost a complete anuria set in.

The Paroxysms. On March 18, 1921, the first attack of paroxysmal tachycardia occurred. The patient complained of abdominal pain, the pulse-rate suddenly rose to 150 per minute, and curiously

became absolutely regular. On the following day she vomited, the heart remained at 150 at the apex and it was noted that all the beats came through at the radials. These regularities of the pulse continued for varying periods during the day and would come and go suddenly. During the next few days the patient continued having tachycardia at irregular periods. By now the edema had increased decidedly, the orthopnea was very distressing, she was very uncomfortable and markedly cyanotic. Up to this time digitalis had been continuously administered in the form of tincture of digitalis, 30 minims thrice daily. This was begun on December 30, and discontinued March 20, 1921. The following day tachycardia had ceased, the pulse was 88 at the apex and 66 at the wrist. It was extremely irregular and numerous extrasystoles were made out. On March 22, the paroxysms returned, but at very irregular intervals. These periods continued until April 9, from which date the tachycardia became constant, the rate varied from 140 to 180 per minute, the pulse remaining constantly regular. The condition of the patient progressively grew worse, the apex of the heart passed out into the posterior axillary line and the liver rapidly enlarged and pulsated. Emaciation became extreme and she died on April 12, 1921. Autopsy was not obtainable.

Electrocardiographic Findings and Discussion. The second series of records (Fig. 2)were made on March 20, 1921, two days after the onset of paroxysms. These showed a very striking and unusual picture, which is best revealed in the third lead. The tachycardia was of sudden onset and was preceded by anomolous deflections identical with those of the paroxysms, and had the appearance of typical ventricular extrasystoles. They arise from both ventricles, and during the paroxysm these anomolous deflections succeed each other alternately in a regular fashion and apparently the stimuli producing the arrhythmia travelled to each ventricle alternately with perfect sequence.

Another series (Fig. 3) of electrocardiograms were obtained on March 23, 1921. The paroxysms were short and came on at irregular periods. The rhythm was extremely irregular between the attacks. This irregularity was the result of groups of extrasystoles forming bigemini or trigemini, and arising from multiple foci. In the third derivation we were fortunate in obtaining a paroxysm. The type of deflections were reproduced with most characteristic exactness, and the picture was identical with that obtained on March 20. During the irregular periods the coupling seen was very much like that of digitalis intoxication, and it is very suggestive that perhaps digitalis was the precipating factor in inducing the paroxysm in our case. Recently, in experiments on cats with intramuscular injections of strophanthin, electrocardiograms were obtained in which a ventricular tachycardia was

induced, and the deflections alternated in a similar fashion, as seen in this patient. (Fig. 4.) Schwensen mentions that Lewis and

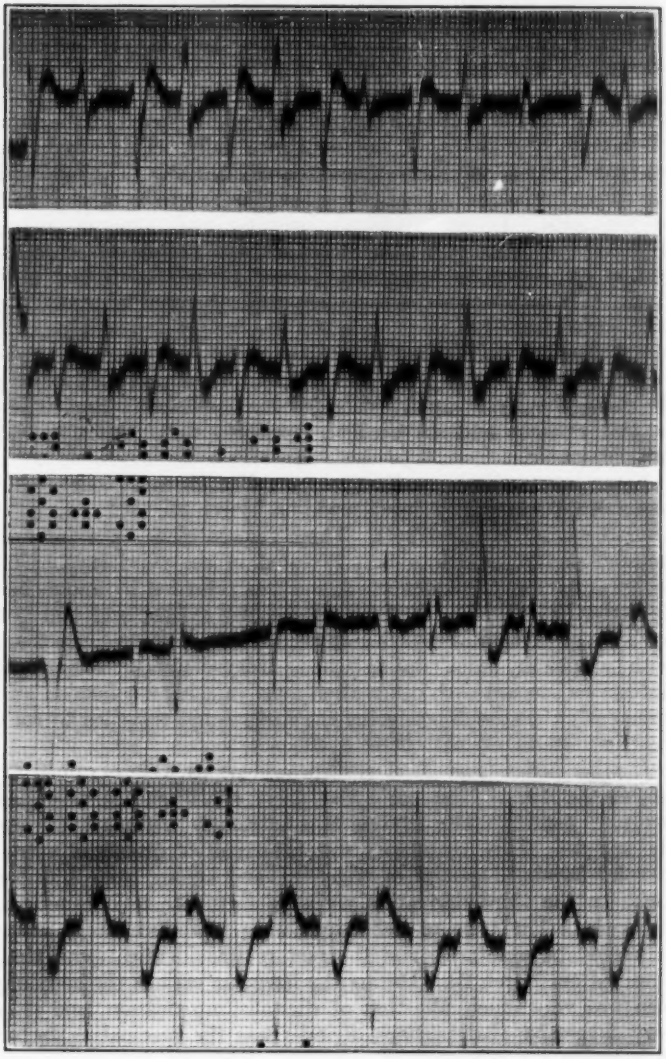


FIG. 2.—Paroxysm recorded March 20, 1921. Leads 1, 2 and 3. In Lead 3 (the last 2 records) the onset of a paroxysm is shown, preceded by premature beats similar to those seen in the continued paroxysm as depicted in the last record.

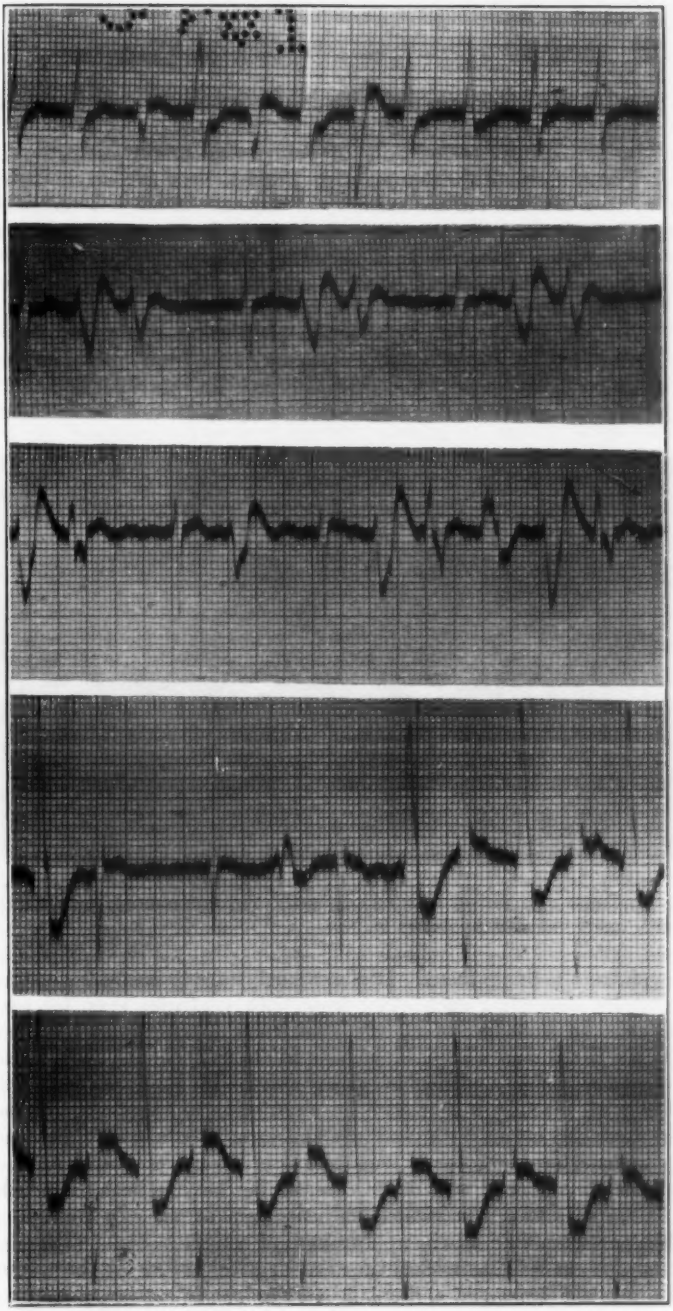


FIG. 3.—Record made March 23, 1921. Heart is beating very irregularly. Leads 1 and 2 show groups of extrasystoles different from the paroxysm, which is recorded in Lead 3. Leads 2 and 3 are each represented by 2 records.

Levy in experiments with chloroform vapors obtained a similar record.

In paroxysmal tachycardia of ventricular origin hitherto described, the site of the dominant rhythm has been in a single center in either ventricle; in the majority of the cases in the left ventricle. In our case, in order to cause this curious picture, as a result of a true ventricular extrasystole, we must assume that there are two independent foci, one in either ventricle, which initiate the contraction alternately in an orderly manner.

Ventricular types of extrasystoles are the more common forms of ectopic beats and in isolated cases may arise from more than one situation in the ventricles, occasionally in both ventricles in a given case. Succession of ventricular extrasystoles are uncommon,

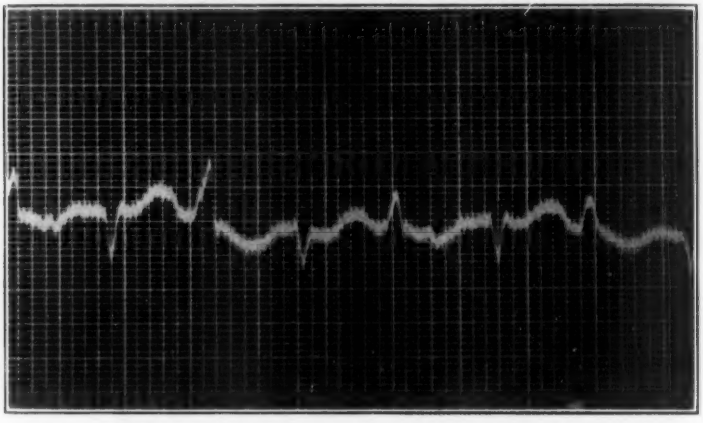


FIG. 4.—Lead 2 of a paroxysm of ventricular tachycardia induced in a cat following injection of .00234 gm. Strophanthin in oil. Cat died suddenly, immediately after record was obtained, August 18, 1922.

even from a single focus. It is extremely rare to encounter extrasystoles succeeding each other from both ventricles even for two beats. In a review of all the ventricular extrasystoles recorded at the Montefiore Hospital, such alternations occur in 2 cases out of a series of 35 ventricular extrasystoles. It is evident from the foregoing discussion that such an alternation of ventricular extrasystoles can occur, both clinically and experimentally but the continuous alternation for a long period is a very rare and unique phenemonon, only one other case so far having been reported. As stated above, the anomalous beats seen in our case preceding the paroxysm had all the appearances of ectopic ventricular beats, and arise in both ventricles; they are identical in form to those seen during the paroxysm, and as the auricles are in a state of fibrilla-

tion and cannot induce a paroxysmal tachycardia, it is unquestionably certain that we are dealing with a ventricular tachycardia.

The mechanism producing this alternation is problematic. A possible theory that suggests itself is that each ectopic center, because of the extreme rapidity of the impulse formation, alternately become exhausted and recovers; so that the pacemaker shifts sequentially in an orderly way from ventricle to ventricle.

Another mechanism which must be recognized as a plausible explanation, in such a case, is that we are dealing with a single focus giving rise to the paroxysm situated somewhere in the main stem of His's bundle, or perhaps, in the auriculoventricular node. Due to defective conduction through these stems of the bundle, the impulse starting the paroxysm is forced to travel down one of the branches. The next impulse coming on rapidly finds this refractory, as it has not had sufficient time to recover, the excitation wave takes the opposite branch and initiates a contraction. By this time the first stem has recovered and is again receptive, while the second branch is now exhausted and refractive; and so the impulse sways from side to side. Against this hypothesis, we must note that both the isolated extrasystoles and the deflections during the attacks have not the appearance usually ascribed to bundle-branch blocks. The time interval is short, only .08 second, and there are no aberrations. Furthermore, if these were levo- and dextrograms, the algebraic summation of the two should give rise to a normal ventricular deflection as presented by the patient. This was not found to be the case when the deflections in three leads were exactly plotted out according to the method described by Lewis.

Conclusions. We have presented a case of paroxysmal ventricular tachycardia in which the impulse travels alternately and regularly through each ventricle. Only one other case of a similar nature has so far been recorded. The mechanism of its production has been discussed. Digitalis intoxication is a possible cause in producing this serious arrhythmia. The danger lies in the transition of the paroxysm into ventricular fibrillation and sudden death.

BIBLIOGRAPHY.

Lewis, T.: Single and Successive Extrasystoles, Lancet, 1909, **1**, 382. Mechanism of the Heart Beat, 1911. Paroxysmal Tachycardia, Heart, 1909–10, **1**, 43. Ibid, 1909–10, **1**, 98.

Lea, E. C.: Auricular Fibrillation with High Degree A.-V. Block and Paroxysmal Tachycardia, Quart. Jour. Med., 1911–12, **5**, 388.

Hart, T. S.: Paroxysmal Tachycardia, Heart, 1912–13, **4**, 128.

Cohn, A. E. and Fraser, F. R.: Paroxysmal Tachycardia and Effects of Stimulation of the Vagus Nerve by Pressure, Heart, 1913–14, **5**, 93.

Butterfield, H. G. and Hunt, G. H.: Observation on Paroxysmal Tachycardia, Quart. Jour. Med., 1914, **7**, 209.

Willius, F. A.: Paroxysmal Tachycardia, with a Special Reference to Tachycardia of Ventricular Origin, Boston Med. and Surg. Jour., 1918, **178**, 40.

Vaughan, W. T.: A Study of Paroxysmal Tachycardia with a Special Reference to Tachycardia of Ventricular Origin, Arch. Int. Med., 1918, **21**, 381.

Hume, W. E.: Six Cases of Paroxysmal Tachycardia of Ventricular Origin, Quart. Jour. Med., 1917–18, **11**, 131.

Gallavardin, L.: Tachycardia paroxystique ventriculaire avec conservation du rhythme auriculaire normale, Arch. des mal. du cœur, 1920, **13**, 121. Tachycardia ventriculaire terminale, Ibid., p. 207. Tachycardia ventriculaire terminale greffée sur une tachysystole auriculaire, Ibid., p. 210.

Robinson, G. E. and Herrmann, G. R.: Paroxysmal Tachycardia of Ventricular Origin and its Relation to Coronary Occlusion, Heart, 1921, **8**, 59.

Schwensen, C.: Ventricular Tachycardia as a Result of the Administration of Digitalis, Heart, 1922, **9**, 199.

Danielopolu, D.: Paroxysmal Tachycardia Due to Digitalis and Strophantus, Arch. des mal. du cœur, 1922, **15**, 537.

COSTODIAPHRAGMATIC ADHESIONS AND THEIR INFLUENCE ON THE RESPIRATORY FUNCTION.

By William S. Middleton, M.D.,

MADISON, WIS.

(From the Department of Clinical Medicine, University of Wisconsin, Madison, Wis.)

By reason of its important anatomical relations and physiological functions, the diaphragm ranks second only to the heart among muscular structures. Its origin from the lower six ribs and their cartilages, the ensiform cartilage and the upper lumbar vertebræ and its insertion, after a dome-like course, into the central tendon, determine the piston action, by which its contraction increases the vertical diameter of the thorax. The dome of this fibromuscular septum is maintained through the negative intrapleural and the positive intraperitoneal pressures. The arc of the dome remains relatively constant in all phases of respiration (except forced inspiration) because of the compensatory changes in pressure upon either side and the moulding of the dome to the underlying liver and spleen.

The share of the diaphragm in respiration has been a mooted point for many years. Obviously, the ascent of the ribs upon inspiration, which leads primarily to an increase in the anteroposterior and lateral diameters of the chest, would appreciably decrease the vertical diameter were it not for the downward sweep of the contracting diaphragm. Its origin from the lower six ribs leads to their fixation on descent of the diaphragm. Fick[1] held that the ascent of the ribs occurring simultaneously with descent of the diaphragm creates an illusion of much greater movement in the latter than actually occurs. Upon this ground alone, he maintained that the inspiratory importance of the diaphragm had been greatly exaggerated. Hutchinson,[2] in discussing his remarkable paper upon vital capacity, expressed the opinion that "ordi-

nary breathing in men was entirely abdominal or diaphragmatic, but the contrary in deep breathing." He felt that inward movement of the anterior abdominal wall upon deep inspiration precluded downward movement of the diaphragm. Sewall and Pollard[3] presented a series of separate vital capacity readings for costal and diaphragmatic respiration in the same individuals. The physical difficulties encountered and the methods of control were not stated. They concluded that the vital capacity of costal breathing is greater than that of diaphragmatic breathing, thus accounting for the increase in the costal type with sudden respiratory stress. Fluoroscopical control of such experiments would seem imperative; under any circumstance, the existence of even normal diaphragmatic tonus would vitiate so-called uncomplicated costal respiration figures.

Expansion of the lower lobes and the dorsal portion of the upper lobes is admittedly dependent upon diaphragmatic contraction.[4] Furthermore, Meltzer[5] showed that intrapleural negative pressure in rabbits increased as the diaphragm was approached. He also determined that changes in intrapleural negative pressure upon inspiration were first and most felt at the base. From these observations, Meltzer divided the lung into surfaces of direct and of indirect expansion. Expanding force would obviously be exerted more markedly on surfaces of direct expansion. Interesting substantiation of this point might be derived from Keith's[4] quotation of Oppel's figures upon the greater dimensions of the basal infundibula (to use the former's obsolete nomenclature), as compared with the apical infundibula, could these data be confirmed in the original source. Unfortunately, reference to Oppel[6] reveals no corroborative figures. (Three years old: Apical infundibula, 0.12 mm.; basal infundibula, 0.38 mm. in diameter. Seventy years old: 0.45 mm. for the apical and 0.85 mm. for basal.) However, Oppel has included identical measurements under Rossignol's tables of dimensions for the different parts of the individual infundibulum ("fundus" and "münding").

Attempts to accurately estimate the part played by the diaphragm in respiration have followed certain mathematical lines. Fick[1] has pointed out that the diaphragm moves 1.5 cm. in quiet respiration and 3 cm. on forced inspiration. Keith[4] determined an area of 250 sq. cm. of the diaphragm to be in contact with the lungs. In this event, a descent of 10 mm. in the diaphragm would increase the thoracic space by 250 cc. Keith concluded that if 400 cc. be taken as the normal tidal air, the diaphragm must be considered a large factor in quiet respiration. Hultkrantz[7] determined a sweep of 10 cm. between the levels of the diaphragm on forced inspiration and forced expiration. He divided the respiratory responsibility of a 490-cc breath into 320 cc from the thoracic movement and 170 cc from the diaphragmatic descent.

From any angle, it must be apparent that the diaphragm plays a considerable part in respiration. Yet not until Hoover[8 9] published his convincing observations upon the activation of the diaphragm was this important structure studied clinically to any degree. The methods of approach to its accurate study are several. The forward thrust of the abdomen upon inspiration has long been considered a measure of diaphragmatic activity. Litten's phenomenon demonstrates clearly the inspiratory descent of the diaphragm. The shape of the dome of the diaphragm may be determined by observation of the changes in the subcostal angle upon inspiration. Opposing the time-honored conclusion of Duchenne,[10] Hoover clearly demonstrated that activation of the diaphragm induced inward movement of the hypochondria. The external intercostal muscles, by their bucket-handle influence upon the ribs, tend to widen the subcostal angle upon inspiration. The sum total of the opposed actions of the intercostal muscles and the diaphragm on the costal margins is slightly in favor of the intercostals, so that with normal relations of the concerned parts there should be slight movement of the costal margins outward upon inspiration. This advantage is easily disturbed by changes in the position of the diaphragm, synechiæ or alterations in the muscular efficiency of either element in this delicate balance. Hence, an increasing importance must be accorded to observations of the changes in the subcostal angle upon respiration. Hoover utilizes this study in determining the form of the diaphragm rather than its gross function.

To these methods of study, based upon inspection, must be added the information gathered by palpation, percussion and roentgenological examination. Palpation will reinforce inspection in the above determinations and to them add the increase in extent of tactile fremitus determined by the increased vertical diameter of the thorax upon the descent of the diaphragm. Percussion will roughly gauge the movement of the diaphragm with respiration. Fluoroscopy is of paramount importance in studying the contour and the extent and regularity of movement of the diaphragm. Roentgenograms have a more limited field in determining the form and the position of this muscle.

Notwithstanding the development of our knowledge of and interest in phrenic function, but few contributions of a clinical nature have been added to the literature. Notable among these have been the roentgenological studies of Pryor.[11 12] By careful fluoroscopical and radiographical observations, diaphragmatic immobility was determined in 53 out of 83 individuals, who had suffered from empyema or pleurisy with effusion, and some restriction of motion was determined in an additional 17. From the etiological standpoint, he found empyema gave the gravest prognosis, 34 of 47 cases studied developing complete unilateral immo-

bility; but pleurisy with effusion showed the same impairment of function in 9 out of 16 cases. Pryor concluded that a diaphragmitis with consequent infiltration, loss of elasticity and muscular atrophy or possibly phrenic neuritis constitute more probable causes of this disabling sequel than do diaphragmatic adhesions.

An unusual opportunity to study the effect of costodiaphragmatic adhesions upon the respiratory function has been afforded in the group of cases under consideration. In the main, they constitute the end-results of thoracic wounds and of empyema. With few exceptions, the routine examination of the diaphragm, as outlined above, was rigorously followed, especial stress being placed upon the study of the subcostal angles and upon fluoroscopy. As a measure of "mobility of the parts concerned in the breathing act,"[2] spirometric readings were made in each instance. The standards based upon height, Hutchinson[2] and Peabody and Wentworth,[13] have been superseded by those derived from body area. The most exhaustive work upon this phase of vital capacity is that of Dreyer;[14] but after a careful analysis of the available standards, West[15] concluded that the average vital capacity for the male is 2.5 liters per square meter of body surface, and for the female 2 liters per square meter of body surface. In this study, West's figures have been used as standard.

Except as otherwise noted in Table I, the diaphragm was totally immobile in all cases. The typical deformity is indicated in Fig. 1. Particular attention is directed to the vital capacity figures, ranging from 57.2 per cent of normal to 75.6 per cent (excluding Case IV), with an average (including Case IV) of 68.1 per cent. Pryor's conclusions of an actual paralysis of the diaphragm was disproved by observations of the movements of the costal margins in this group. Invariably, there was either slight movement of the costal margins toward the midline or no movement whatever upon inspiration. Hoover ascribed this phenomenon to the mechanical advantage of a more direct line of phrenic contraction. In effect, the points of origin and insertion of the diaphragm have been approximated more closely and the arc of contraction effaced by obliteration of the costophrenic sulcus through adhesions. This evidence of an ascendency of the diaphragm over the intercostal muscles in their action upon the costal margins is proof of phrenic contraction. Then, too, in event of unilateral paralysis, the affected leaflet should be elevated upon inspiration because of the unopposed increase in abdominal pressure from descent of the intact leaflet. In no case was this balance movement noted.

For comparison with this group of complete unilateral diaphragmatic immobility, a second group of 6 cases with impaired mobility was collected. The wide fluctuations in vital capacity readings (71.7 to 102.2 per cent) in such a limited number of cases vitiate their significance. However, the average reading was 87.6 per cent of normal.

TABLE I.—INCLUDING CASES OF PRACTICALLY COMPLETE UNILATERAL DIAPHRAGMATIC IMMOBILITY.

	Case.	Roentgenray findings.	Body area.	Vital capacity.	Per cent. normal. (West.)
I.	Influenza-empyema (thoracotomy)	Complete obliteration costophrenic sulcus	1.7	2550	60.0
II.	Influenza-empyema recurrent (thoracotomy	Diaphragm adherent to seventh rib laterally	1.9	2750	57.8
III.	Influenza-tuberculosis (pneumothorax)	High adhesion diaphragm; pneumothorax, partial	1.8	3375	75.0
IV.*	Influenza-empyema (thoracotomy)	Diaphragm adherent to eighth rib; sulcus obliterated; central dipping	1.8	4000	88.8
V.	G. S. W., rt. shoulder, empyema (thoracotomy)	Complete obliteration costophrenic sulcus	1.85	3500	75.6
VI.	Influenza-empyema (thoracotomy)	Costophrenic sulcus obliterated	1.55	2375	61.2
VII.	G. S. W. (sucker) empyema (thoracotomy)	High diaphragmatic adhesions; obliterated sulcus; little central movement	1.75	3200	73.1
VIII.	G.S.W.;-penetrating empyema (thoracotomy)	High adherent diaphragm	1.85	2650	57.2
IX.	G. S. W.—T. and T. (thoracotomy)	Obliteration costophrenic sulcus with little motion	1.65	2400	58.1
X.	G.S.W., penetrating (thoracotomy), retained F. B.	Small partial pneumothorax; obliterated sulcus, little motion	1.8	2900	64.4
XI.	G.S.W., penetrating (thoracotomy)	High adhesion diaphragm; narrow sulcus, little motion	1.8	3400	75.5
XII.	G.S.W., penetrating (F.B. retained)	High adhesion diaphragm; narrow sulcus, central flattening	1.9	2950	62.1
XIII.	G.S.W., penetrating (thoracotomy)	Obliterated sulcus	1.65	3000	72.7
XIV.	G.S.W., sucker (thoracotomy) pneumonia-empyema	High adhesions diaphragm; obliterated sulcus	1.95	3500	71.7
XV.	G. S. W.—T. and T. (thoracotomy)	Obliterated sulcus	1.75	3000	68.5

From the data advanced, costophrenic synechiæ, obviously, constitute a considerable embarrassment to respiration. A reduction of 31.9 per cent in vital capacity while a serious respiratory handicap, is probably still an inadequate measure of the respiratory interference of unilateral fixation of the diaphragm; for the existence of any degree of tonus in the fixed muscle will have reduced the handicap somewhat by aiding inspiration. Further-

* Case IV is an interesting commentary upon the efficacy of continued conscientious breathing exercises. Of an athletic type this individual has practised forced or opposed breathing daily for the past three years.

more, compensatory intercostal effort upon the side of the fixed diaphragm and contralateral increase in both intercostal and diaphragmatic activity are to be anticipated on fixation of one diaphragmatic leaflet by adhesions. Therefore, the percentage reduction in vital capacity, above stated, has been favorably influenced by other factors, and the actual uncompensated decrease would be greater.

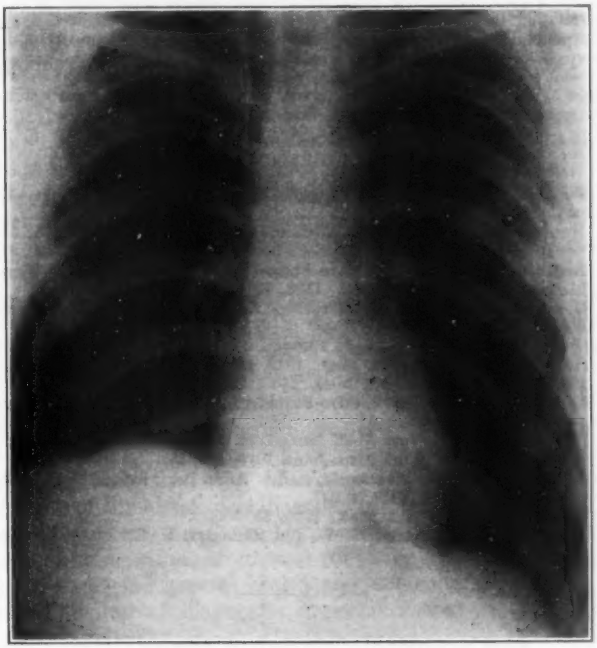


FIG. 1.—Typical phrenic deformity.

Conclusion. It would seem apparent that the part of the diaphragm in deep respiration has been underestimated. From the present vital capacity studies, which clearly minimize the actual influence of a unilateral fixation of the diaphragm upon respiratory function, the normal diaphragmatic contraction must account for at least 60 per cent of the respiratory interchange in deep breathing. Tidal-air observations are impossible in the human; but the recent work of Drinker, Peabody and Blumgart[16] suggests the possibility of determining, by animal experimentation, the influence of unilateral phrenoplegia and fixation on this phase of respiration.

Protection of the diaphragm from needless trauma and continued contact with inflammatory products will limit the occur-

rence of disabling costophrenic synechiæ. Lastly, avoidance of protracted diaphragmatic immobility is essential for a complete restoration of function. Early and continued breathing exercises are advised in all cases of pleural inflammation involving the diaphragm.

NOTE.—Since this paper was submitted for publication, Hoover has reported the results of his studies on the action of the intercostal muscles in the *Journal of the American Medical Association*, 1922, **30**, 1. One finding in particular is of interest in relation to the present work. Hoover induced a pronounced hyperpnea in experimental dogs by having them breathe an atmosphere rich in carbon dioxide (25 per cent). On phrenic section in such animals a reduction in vital capacity of 50 per cent was remarked. This finding would be most significant, if it were found constant by repeated experiments, even though subsequent laparotomy determined in the instance reported above, contraction of the crura.

REFERENCES.

1. Fick, R.: Handbuch der Anatomie und Mechanik der Gelenke, Dritter Teil, 1911.
2. Hutchinson, J.: Proc. Royal Med. and Chir. Soc., Lancet, 1846, **1**, 630.
3. Sewall and Pollard: Jour. Physiol., 1890, **11**, 159.
4. Keith, A.: Further Advances in Physiology (Leonard Hill ed.), 1909, p. 182.
5. Meltzer, S. J.: Jour. Physiol., 1892, **13**, 218.
6. Oppel, A.: Lehrbuch der mikroskop. Anatomie der Wirbeltiere, Sechster Teil, 1905, p. 642.
7. Hultkrantz: Skandinav. Arch. Physiol., 1890.
8. Hoover, C. F.: Arch. Int. Med., 1913, **12**, 214.
9. Hoover, C. F.: Arch. Int. Med., 1917, **20**, 701.
10. Duchenne: Récherches Electro-Physiologiques et Thérapeutiques sur la Diaphragme, 1853.
11. Pryor, J. H.: New York Med. Jour., 1916, **103**, 10.
12. Pryor, J. H.: New York Med. Jour., 1916, **103**, 781.
13. Peabody, F. W., and Wentworth, J. A.: Arch. Int. Med., 1917, **20**, 443.
14. Dreyer, G.: Lancet, 1919, **2**, 227.
15. West, H. F.: Arch. Int. Med., 1920, **25**, 306.
16. Drinker, C. K., Peabody, F. W., and Blumgart, H. L.: Jour. Exp. Med., 1922, **35**, 77.

THE DIAGNOSIS OF TUBAL PREGNANCY.

BY EMIL NOVAK, M.D.
BALTIMORE, MD.

(From the Gynecological Department of Johns Hopkins Medical School.)

THERE are many cases in which the clinical picture presented by extrauterine pregnancy is so classical that its diagnosis is almost compelling. In others, again, its recognition before operation is exceedingly difficult, in spite of the most careful study of the patient's history and the most thorough physical examination. Even when the diagnosis seems quite clear, the surgeon not infrequently meets with surprises on opening the abdomen, for, as will be discussed below, there are a number of other conditions which

may almost perfectly mimic the clinical picture of this disease. On the other hand, even more frequently operation reveals extrauterine pregnancy in cases in which its existence had not even been thought of. The general practitioner or the gynecologist who would avoid too many humiliating surprises of this sort must have the possibility of this condition constantly within his field of vision.

The diagnosis of extrauterine pregnancy is usually considered under two heads, viz.: (1) The diagnosis before rupture and (2) the diagnosis after rupture. This plan does not appeal to me as a very wise one, for small and perhaps repeated ruptures of the pregnant tube often occur with such slight symptoms as to defy recognition. Indeed, it is relatively rare to operate upon cases in which there has been no internal hemorrhage whatsoever, either from rupture of the tubal wall or from tubal abortion, and even more rare to operate before at least some intratubal bleeding.

The clinical picture in the unruptured cases, or in those with moderate intraperitoneal bleeding, is quite different from that characterizing those cases in which the internal bleeding is sudden, overwhelming, and cataclysmic. For this reason, it would seem wiser to group the cases, from the standpoint of diagnosis, into (1) the nontragic type—those with moderate internal hemorrhage or none at all; and (2) those of the tragic or cataclysmic variety, where hemorrhage is sudden and perhaps overwhelming. I may say that in this brief paper I shall not attempt to discuss the less common forms of extrauterine pregnancy, nor shall I consider the diagnosis of such sequelæ as secondary abdominal pregnancy, lithopedion formation, etc. Moreover, I shall not enter into any discussion of the histological diagnosis of tubal pregnancy.

1. The Non-tragic Type. It is in this group of cases that the problem of diagnosis is often most confusing. Patients of this type are often in good general health and not confined to bed. The principal points of diagnostic importance may be briefly summarized as follows:

(*a*) *Menstrual Irregularity.* It was formerly stated that as a rule one or more menstrual periods, usually one, are skipped, following which uterine bleeding begins and is kept up more or less constantly. My own experience, however, like that of a number of recent authors, has been that menstruation is not skipped at all in a large proportion of cases. In Farrar's cases[1] only 34 per cent showed an amenorrhea. This is the same figure given by Wynne[2] in his exhaustive study of 303 cases from the Gynecological Clinic of Johns Hopkins Hospital. Other authors, however, put the figure much higher (MacKenzie[3] at 75 per cent, Rongy[4] at 71 per cent). It is not uncommon to find that the menstrual period is actually anticipated by from a few days to perhaps even two or three weeks.

Perhaps even more characteristic than the short period of amenor-

rhea which often occurs, is the uterine bleeding which then puts in its appearance. Most often the bleeding is scanty and "spotting" in type, and is associated with crampy pains in one side or the other of the lower abdomen. Rarely is the hemorrhage free, and almost never alarming. This is a point of some diagnostic importance in the differentiation between tubal pregnancy and incomplete abortion of a uterine pregnancy. In the latter, as is well-known, bleeding may be exceedingly free, so that the patient may soon be almost exsanguinated. This is almost never the case with the external bleeding of extrauterine pregnancy. Some authors lay stress upon the abnormal brownish color of the bloody discharge seen with extrauterine pregnancy, but I do not believe that this sign will often prove of value.

Bleeding of the type described is an almost constant symptom with ruptured tubal pregnancy. It was present in 67.4 per cent of Farrar's cases. In a rather large experience I have seen only a few cases in which this symptom was lacking. In one of these, a patient referred by Dr. B. S. Rankin, of Tunnelton, W. Va., there had been complete amenorrhea for two months, after which the patient began to suffer with violent pains in the left iliac fossa, associated with syncopal attacks. A large sensitive mass filled the left side of the pelvis at the time of operation. A diagnosis of ruptured left tubal pregnancy was made, in spite of the absence of uterine bleeding. This was confirmed at operation. Six weeks after the operation the patient expelled a three months' fetus from the uterus. It had been a case of combined intra- and extrauterine pregnancy, the uterus being pregnant at the time of removal of the tube. There can be no doubt that the presence of the live fetus in the uterus was the explanation of the absence of uterine bleeding. In two other cases, which I have previously reported, the fetus was apparently alive at the time of operation. To put it conversely, I believe that the death of the fetus is the responsible factor in the causation of the uterine hemorrhage.

This is the logical explanation if one recalls the mechanism of normal menstruation. The corpus luteum, through its internal secretion, calls forth the characteristic hypertrophic changes seen in the endometrium just before menstruation. It has nothing to do, however, with the actual bleeding of menstruation, which does not begin, as a matter of fact, until the influence of the corpus luteum is inhibited or counteracted by some other factor—most likely the death of the ovum which was thrown off at the preceding ovulation. There are other facts which point to the death of the unimpregnated ovum as a cause of the bleeding of normal menstruation and to the death of the impregnated ovum, *i. e.*, the fetus, as a cause of the bleeding in either intra- or extrauterine pregnancy.

Certainly this theory is more plausible than that recently suggested by Polak,[5 6] who believes the hemorrhage is the result of

"ovular unrest" caused by hemorrhage around the ovum in the tube, and that the tubal peristalsis thus excited is transmitted to the uterus, thus disturbing the decidua and causing bleeding. Cases like the three mentioned above in this paper as being unaccompanied by hemorrhage would seem to be sufficient refutation of this theory. In all of these there was certainly sufficient distention of the tube to excite peristalsis, and yet there was no bleeding, even in the case where there was an associated intrauterine pregnancy.

(*b*) *Pain.* With few exceptions pain is a prominent symptom, usually the most prominent symptom, in cases of tubal pregnancy. Its frequency as a symptom is put variously at from 80 to 96.6 per cent of all cases. The explanation of the pain is no clearer than our still imperfect knowledge of the mechanism of pelvic pain in general. Whether it be due to increased tubal peristalsis or to the congestion of the parts, whether the pain stimuli are perceived in the tube itself, or whether they are really referred to the somatic nerves of the parietal wall, according to the segmental theory of Head—these are still points, concerning which we cannot speak dogmatically. There is a little reason to doubt, however, that the sudden attacks of colicky pain associated with faintness or actual syncope are the result of ruptures and internal hemorrhages of varying degrees of severity. Here the pain and the faintness are perhaps both in large measure due to the contact of the escaping blood with the peritoneum.

Broun,[7] in an interesting comparison of the history and the operative findings in cases of tubal pregnancy, found in a series of 55 cases, that 22 in which there was a history of sharp severe pain showed at operation an escape of free blood into the peritoneal cavity. In another group of 20 cases the pain was chiefly pelvic, and was described as varied in character and degree. In these the blood in the pelvis was found to be encapsulated. In still another group of 7 cases, the only pain was a slight discomfort in the involved side, and here there was no extratubal bleeding at all. These findings are practically similar to those of Farrar, who states that "in only 18.8 per cent of cases was the pain of the character ordinarily considered peculiar to ectopic gestation. In the remaining cases it was not to be differentiated from that of any severe pelvic lesion."

(*c*) *Findings on Pelvic Examination.* The demonstration of a one-sided mass in the pelvis is little less than a *sine qua non* in the diagnosis of tubal pregnancy. There is a small proportion of cases where the suspicion is strong in spite of the absence of this finding, but here great caution is necessary to avoid embarrassing mistakes. Farrar found a unilateral pelvic mass in no less than 96 per cent of her cases, and other authors (Frank, Oastler) give percentages almost as high. The usual statement is that the mass is exquisitely tender. My own experience has been that there are not infrequent

exceptions to this rule, and that in a certain number of cases the mass is not any more tender than many of those encountered in connection with pelvic inflammatory disease.

Enlargement of the uterus is usually slight or perhaps not discernible at all. On the other hand, when the uterus is much enlarged the existence of intrauterine pregnancy may be reasonably assumed.

(*d*) *Other Symptoms.* While the signs and symptoms already described are those upon which the diagnosis of extrauterine pregnancy will usually depend, there are a number of others which not infrequently throw considerable light on the individual case. For example, the subjective symptoms of pregnancy are often observed by the patient, more especially before the occurrence of rupture of the gestation sac. Often, however, they are only slightly or not at all noticeable. This applies to such symptoms as nausea and vomiting, increased frequency of urination, etc. The previous history of the patient is often suggestive, especially if she has apparently become pregnant after a long period of sterility. One child sterility especially is apt to be followed by tubal pregnancy. About 30 per cent of all cases of the latter, according to MacKenzie, give such a history. The explanation of this predisposition is simple enough when one recalls the frequency with which tubal inflammation is lighted up by pregnancy, and the etiological importance of tubal obstruction in the production of tubal gestation. From the same point of view, considerable importance attaches to a history of previous pelvic operations, because of the frequency with which these cause mechanical obstruction of the tube lumen by external adhesions or obliterative inflammatory processes. The passage of bits of decidua is suggestive, but will scarcely permit of differentiation from intrauterine pregnancy with abortion. Besides, this occurrence is not observed in the great majority of cases.

Tragic Cases. Fortunately, only a small proportion of all cases of tubal pregnancy—probably about 5 per cent—are encountered in the so-called tragic or cataclysmic stage. In these it is at times possible to elicit a history of one or more previous attacks of colicky pain, together with faintness or actual syncope, indicating perhaps repeated smaller hemorrhages before the real deluge. In other cases the patient has had little or no previous warning, having perhaps noted only a slight amount of abnormal uterine bleeding and a moderate discomfort in one or other lower abdominal quadrant. With the sudden onset of massive hemorrhage there occurs a sharp lancinating pain in the involved side of the pelvis, weakness, syncope, extreme pallor, rapid thready pulse, a cold clammy skin, sighing respiration, etc.—in short, all the classical symptoms of alarming internal hemorrhage. Frequently the abdomen becomes full and rounded, especially in women with lax abdominal walls. Contrary to Schumann and DeLee, I have quite frequently been able to elicit dulness in the flanks on percussion.

In cases in which the patient is not seen until the lapse of a good many hours, careful inspection of the umbilicus will often show the presence of the "blue belly-button sign" of Cullen.[8] I have fully discussed and pictured this important sign in a recent article in the Journal of the American Medical Association.[9] It was first described by Cullen in 1919. Its presence makes the assumption of intra-abdominal hemorrhage highly probable. It is of course not pathognomonic of ruptured extrauterine pregnancy, as I took pains to emphasize in my original article. In addition to the 2 cases reported in the latter I have since then observed the sign in two other patients in whom operation disclosed ruptured tubal pregnancy. Where there is a history of menstrual irregularity, sudden unilateral pelvic pain, with symptoms of internal hemorrhage, either with or without the presence of a definite pelvic mass, the demonstration of Cullen's sign makes the diagnosis of ruptured tubal pregnancy almost absolutely certain. In view of the probable cause of this sign—lymphatic absorption of blood pigment—it is obvious that it may in exceptional cases occur in association with other conditions. But this does not militate against its importance as a diagnostic sign in cases where there are other symptoms suggestive of ruptured extrauterine pregnancy. It is true that in most of these the diagnosis can be made with reasonable certainty without the aid of Cullen's sign, but at times the picture is not so clear-cut, and one is grateful for every ray of light that can be thrown on the problem. I make this explanation because one or two authors, apparently under the erroneous impression that the sign had been described as pathognomonic of ruptured extrauterine pregnancy, have taken the trouble to report cases illustrating the obvious fact that occasionally it may occur with other conditions.

The blood picture in cases of the tragic type is often of importance in diagnosis. Where the hemorrhage is severe, there is usually a high leukocytosis, which develops very soon after the onset of the bleeding. The hemoglobin percentage is of course diminished, but the figure can in no way be considered as an index of the amount of bleeding, inasmuch as it requires many hours for the hemoglobin to drop to its lowest point, as Schumann[10] has emphasized.

Differential Diagnosis. It is of course possible to mistake extrauterine pregnancy for any one of a multitude of other pelvic or abdominal conditions, and *vice versa*. There are only a few, however, in which this problem of differentiation presents itself with great frequency, and I shall therefore discuss only the two or three which would seem to be of greatest practical importance in this connection.

Threatened or incomplete abortion of uterine pregnancy. Perhaps the greatest number of diagnostic errors are made in the differentiation between tubal pregnancy and abortion of normal intrauterine pregnancy. This distinction is obviously of the greatest

importance, because of the very different therapeutic procedure called for in the two conditions. It may be a serious thing to curette, and merely to curette, a case of tubal pregnancy, and likewise it would be unfortunate to subject a patient to laparotomy in a case of simple miscarriage. In either case a patient may give a history of skipping one or more periods, and then beginning to bleed more or less continuously. There may be pain with a miscarriage, but it is less severe than with an ectopic pregnancy, and is rarely unilateral. The diagnosis is, after all, dependent upon the pelvic examination. In the case of a threatened miscarriage, after the first few weeks of pregnancy the uterus is apt to be much larger than with an ectopic. However, in cases of incomplete abortion where the uterus has almost emptied itself, the organ may show little or no enlargement, as with ectopic pregnancy.

Most important of all is the finding of a unilateral tender mass with ectopic gestation and the negative finding in the adnexa with normal pregnancy. In most cases the distinction is thus easily made, but it is at times more difficult, as in very stout or very nervous women. It is not surprising, therefore, that many mistakes of diagnosis have occurred. Not a few women have been subjected to laparotomy unnecessarily, while on the other hand in many cases curettage has been performed in cases of extrauterine pregnancy, with sad results. I recall rather vividly a comparatively recent case in which I was called upon to open the abdomen of a woman who had, a few hours previously, been curetted for what had been presumed to be an early miscarriage. After the curettage the woman's pulse became rapid, her skin became pale, and, in short, she quickly developed symptoms of alarming internal hemorrhage. This impression was confirmed by the operation, for the abdomen was full of blood. The source of the latter was a tubal rupture, evidently caused by the trauma of the curettage. The patient barely escaped with her life. The same danger of rupturing the gestation sac must be borne in mind in making the usual examinations, especially under anesthesia, when the protective rigidity of the abdominal wall is done away with. There are few teachers of gynecology who cannot recall such mishaps as a result of pelvic examinations made by students.

Acute Pelvic Inflammatory Disease. In cases of acute salpingitis, especially of the gonorrheal type, there is a tendency for a suppression of the menstrual function. Usually one period is thus skipped, and then, after a period of a number of days, uterine bleeding puts in an appearance. Pelvic pain is the rule, and it may be much more severe on one side than the other, while bimanual examination may show a one-sided mass, where the involvement is still confined to one side. It will thus be seen that the picture of ectopic pregnancy may be very closely simulated.

As a rule the diagnosis is made possible by the history of a possible

gonorrheal, postabortive or puerperal, infection, by the existence of a much higher fever with the inflammatory disease than is common with ectopic pregnancy, or by the fact that the pelvic masses are bilateral, as they usually are with inflammatory disease. When bleeding is present with salpingitis, it is rarely associated with sudden attacks of faintness, as with ectopic pregnancy, and there is no history of subjective signs of pregnancy. Such points of differentiation will as a rule enable one to make a correct diagnosis, but in a certain proportion of cases the distinction between the two conditions is very difficult, and mistakes frequently occur.

Ovarian Cysts (especially corpus luteum cysts). As a rule, ovarian cysts are not likely to be confused with tubal pregnancy, inasmuch as, with the exception of corpus luteum cysts, they do not usually give rise to the menstrual disturbance and the pain so characteristic of the latter. I have seen a number of cases in which mistakes in diagnosis were made because of the coexistence of intrauterine pregnancy and unilateral ovarian cysts. The occurrence of abortion in such a case will create a clinical picture which is at times almost indistinguishable from tubal gestation—pain, uterine bleeding following amenorrhea, a unilateral pelvic mass, etc. Examination under anesthesia will often help materially in settling the question, permitting of easier outline of the usually ovoid, nicely circumscribed ovarian cyst. Curettage, of course, is of decisive importance. The gross or microscopical recognition of placental elements is proof positive of intrauterine pregnancy.

It is the corpus luteum cyst, however, which is of the greatest interest and the greatest importance in this connection, for it is this variety which is especially apt to simulate almost perfectly the clinical picture of ectopic gestation. There is still much to learn concerning the relation of the corpus luteum cyst to the corpus luteum of menstruation and the corpus luteum of pregnancy. Certainly it would seem fairly clear that the function—or at least one of the functions—of active lutein cells is to inhibit menstrual bleeding, although they are responsible for the premenstrual or pregravid hypertrophic changes in the endometrium. It is hence not surprising that the corpus luteum cyst, with its lining of lutein cells, often causes a period of amenorrhea. Only a single period is usually missed, and then in from a few days to a few weeks, there begins an irregular uterine hemorrhage, which like that of ectopic pregnancy, is usually scanty in amount and perhaps associated with some pain. Added to this is of course the presence of an enlargement in one side of the pelvis. It is easy to understand, therefore, why mistakes in diagnosis have often occurred.

Other Conditions. Occasionally, the clinical picture of ruptured extrauterine pregnancy is almost exactly reproduced by intra-abdominal hemorrhage from a corpus luteum or a follicular cyst. I reported a striking case of this type in 1917,[11] and collected 84

similar cases from the literature. Since then a number of other instances of this occurrence have been recorded, so that, in spite of its comparative rarity, its possibility should be borne in mind.

There are a number of other conditions which may at times be confused with tubal pregnancy—appendicitis, ovarian cyst with twisted pedicle, etc. With these, however, the differentiation is as a rule easier than with those which have been considered, so that they may be passed with mere mention.

Summary. 1. The diagnosis of tubal pregnancy is at times exceedingly easy, at other times very difficult or perhaps impossible.

2. Diagnosis will be most frequently made by those practitioners who are constantly on the alert for it.

3. The conditions from which tubal pregnancy, of the non-tragic type, is most frequently to be differentiated are pelvic inflammatory disease, threatened or incomplete abortion of an intrauterine pregnancy, and unilateral ovarian cysts, especially of the corpus luteum variety.

4. The most important diagnostic symptoms are the menstrual history, the pelvic pain and the presence of a unilateral tender mass in the pelvis.

5. The diagnosis of the tragic or cataclysmic cases is as a rule comparatively simple. At times it may be difficult or impossible to distinguish cases of this group from the occasional instances of intra-abdominal hemorrhage due to the rupture of a corpus luteum or follicular cyst. More rarely they are mistaken for such conditions as acute appendicitis, ovarian cyst with twisted pedicle, etc. The "blue belly-button" sign of Cullen is often of value in the recognition of intra-abdominal hemorrhage, which is most often due to ruptured ectopic pregnancy.

REFERENCES.

1. Farrar, L. K. P.: An Analysis of 309 Cases of Ectopic Gestation in the Woman's Hospital in the State of New York, Am. Jour. Obst., 1919, **79**, 733.

2. Wynne, H. M. N.: Ectopic Pregnancy, Bull. Johns Hopkins Hosp., 1919, **30**, 15.

3. MacKenzie, S. N.: The Clinical Aspects of Extrauterine Gestation, Jour. Obst. and Gynec. Brit. Emp., 1911, **20**, 277.

4. Rongy, A. J.: The Treatment of Ectopic Gestation, Based on a Study of 100 Cases, Am. Jour. Obst., 1918, **77**, 86.

5. Polak, J. O.: Observations in 227 Cases of Ectopic Pregnancy, Am. Jour. Obst., 1915, **71**, 946.

6. Polak, J. O. and Welton, T. S.: A Study of the Origin of Bleeding in Ectopic Pregnancy, Am. Jour. Obst. and Gynec., 1922, **3**, 164.

7. Broun, Le R.: Menstrual Disturbance and Pain in Tubal Pregnancy, Med. Rec., 1921, **100**, 839.

8. Cullen, T. S.: Bluish Discoloration of the Umbilicus as a Diagnostic Sign where Ruptured Extrauterine Pregnancy Exists. Contributions to Medical and Biological Research, Dedicated to Sir William Osler, in Honor of his Seventieth Birthday, July 12, 1919.

9. Novak, Emil: Bluish Discoloration of the Umbilicus in the Diagnosis of Ruptured Extrauterine Pregnancy, Jour. Am. Med. Assn., 1922, **78**, 643.

10. Schumann, E. A.: Extrauterine Pregnancy, Appleton & Co., New York, 1921.

11. Novak, Emil: Abdominal Hemorrhage of Ovarian Origin, Jour. Am. Med. Assn., 1917, **68**, 1160.

THE ALKALI RESERVE OF THE CEREBROSPINAL FLUID IN VARIOUS STATES OF THE CENTRAL NERVOUS SYSTEM.

By Raphael Isaacs, M.A., M.D.,

INSTRUCTOR IN MEDICINE, COLLEGE OF MEDICINE, UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

The intimate relation of the cerebrospinal fluid and the tissues of the brain and cord suggests that a study of the chemistry of the fluid may throw some light upon the physiology and pathology of states of the central nervous system. The present paper, which deals with the relation of the carbon-dioxide combining power of the cerebrospinal fluid to various symptoms, signs and diseases, is based upon a study of 110 cases, with 156 analyses of cerebrospinal fluid and 62 of the blood, from patients in the Cincinnati General Hospital.

Material and Methods. The specimens of spinal fluid and blood were collected during the course of the clinical study of each case. The cerebrospinal fluid was obtained by lumbar and cistern puncture and the blood from the arm veins. Several methods of collection and preservation were tried. In most cases the examination was made within fifteen minutes. In others the test-tubes were plugged with rubber stoppers and put in the ice-box. Some specimen tubes were plugged with cotton stoppers only. The best method was found to be to cover the freshly drawn spinal fluid with sterile liquid petrolatum to a depth of 2 to 3 cm. Cell counts were always made on freshly drawn fluid. The oil method preserved the original reaction and alkali reserve for long periods, especially when kept on ice. Fluids preserved with toluol showed the same alkali reserve for weeks unless the glass tubes were very soluble. For determining the reaction to phenolphthalein or phenolsulphonephthalein, the freshly drawn fluid, or that drawn under oil, was used. The carbon-dioxide combining powers of the spinal fluid and of the blood plasma were determined by the method of Van Slyke, using the mercury burette. Clinical observation as well as the chemical analyses, except the Wassermann tests, were made by the author, so that the technic in each case was uniform and of value for purposes of comparison.

For fractional analysis, 2 to 5 cc (occasionally more) were collected in separate tubes, the tubes being numbered in the order in which the fluid came out. The term "lowest fraction" is used to indicate the first fluid that came out.

Data. In the study of the fluids, it was found that in some cases the first fluid withdrawn differed from the succeeding fractions, indicating that the carbon-dioxide combining power differed in the fluid surrounding different regions of the brain and cord. The

following two tables show the results when the first fraction (usually the first 5 cc) was used. The results of the fractional analysis are given later.

TABLE I.—CARBON-DIOXIDE VOLUMES PER CENT IN SPINAL FLUID AND BLOOD PLASMA.

	Spinal fluid.			Blood plasma.			Blood plasma relation to spinal fluid.		
	No. of cases.	Range.	Av. vol.%.	No. of cases.	Range.	Av. vol.%.	Higher.	Lower.	Similar.
Mentally normal	32	28–60	50.71	21	29–66	50.30	11	9	1
Unconscious	19	11–65	39.50	8	32–68	47.62	3	4	1
Convulsions	8	32–53	43.37	2	46–48	47.00	2		
Delirium, mania	6	34–55	41.66	1	..	39.00	1		
Headache	10	1–52	38.90	5	32–60	46.20	3	1	1
Semicomatose, hazy, drowsy	44	6–79	41.58	18	33–56	46.70	11	5	0

TABLE II.—CARBON-DIOXIDE VOLUMES PER CENT IN SPINAL FLUID IN RELATION TO VARIOUS TESTS.

	No. of cases.	Range.	Av. vol. %.
Wassermann negative*	67	22–79	49.10
Wassermann positive†	9	16–62	44.30
Globulin normal	47	22–60	45.87
Globulin increased	50	16–79	41.14
Pressure normal	47	24–61	49.36
Pressure increased	65	6–65	42.00
Cell count normal‡	24	36–60	48.50
Cell count above 8	54	16–79	43.10
Alkaline to phenolphthalein	17	34–66	45.60
Acid to phenolphthalein	35	23–55	38.80

* Spinal negative, blood positive, 8 cases, both negative 37.

† Spinal positive, blood negative, 0 cases, both positive 7.

‡ The majority of those with a normal cell count occurred between 50 and 56 with the maximum at 51 and 52. The majority of the abnormals occurred between 33 and 56, with the maximum between 46 and 48. The cell counts varied at different levels; in one case (F 5932) the ventricular fluid showed 27 cells, while fluid from lumbar puncture showed 400 cells.

Only those fluids were recorded in these calculations which were taken under ideal conditions, without loss of carbon dioxide. The occurrence of fluids alkaline to phenolphthalein was unexpected in so large a proportion, but it was found that fluids at one level could be "acid," while at another level they could be alkaline to phenolphthalein. The following cases show some of the variations:

F 7955.—Lowest fluid acid to phenolphthalein, higher fluids alkaline. (Cerebrospinal lues, septicemia.)

F 5932.—Lowest fluid acid to phenolphthalein, higher fluids alkaline. (Tuberculous meningitis.)

In this case 1 cc of phenolsulphonephthalein solution injected into the ventricles. A lumbar puncture later showed the first fluid to be yellow and the later fractions pink. The yellow tube turned pink on addition of alkali, showing that the color was caused by the phenolsulphonephthalein and that the lowest portion was acid (below p^H 7) and the upper portions were alkaline to this indicator.

F 8215.—Lowest fluid alkaline (CO_2 combining power, 52); after 8 cc the fluid was intensely alkaline (CO_2 combining power, 66). (Cerebrospinal lues.)

F 8823.—Fractions, totalling 25 cc, all acid to phenolphthalein.

F 8833.—(1) Fractions all acid, totalling 30+ cc. Later: (2) first 5 cc, just alkaline; third 5 cc, less alkaline; fourth 5 cc, very alkaline. (CO_2 combining powers, 40–40–39; the most alkaline had a slightly lower carbon-dioxide combining power.) (Encephalitis lethargica.)

F 8885.—Lowest alkaline, middle acid, highest alkaline (5 cc fractions). (Carbon-dioxide combining power, 44–43–49.) (Cerebrospinal lues.)

F 9732.—Lowest fraction acid, highest alkaline (total 19 cc). (Skull fracture.)

F 9918.—Second 5 cc fraction slightly alkaline; fourth 5 cc fraction, acid. (Miliary tuberculosis.)

G 3031.—All fractions (total 50 cc) acid to phenolphthalein. They were alkaline to phenolsulphonephthalein, this degree being represented as follows: First 15 cc, +; second 15 cc, +++; third 15 cc, ++; fourth 5 cc, ++. (Miliary tuberculosis.)

F 9769.—Fluid obtained by cistern puncture was acid to phenolphthalein.

F 9151.—Fluids contaminated with blood usually were alkaline. Lowest 8 cc acid, highest 7 cc (of 15 cc) alkaline. (Two middle fractions had carbon-dioxide combining powers of 32, but the upper was alkaline and the lower acid.)

In 15 determinations in *encephalitis lethargica*, the average during the acute manifestations was 48.85, with a range from 37 to 79 in the fluid from the lowest part of the canal. Fluids from successively higher levels in one case showed 37–32–32–34–32 (portions of 5 cc each), with a difference of 5 volumes per cent between the lower and the upper 5 cc (a difference of 30 to 40 cc) in the spinal canal. Another determination showed 40–40–x–x–39 for the successive levels. There was some tendency for the highest fluid to have the lowest carbon-dioxide combining power. In a case in which the fluid (lowermost) was followed during three periods up to recovery, there was an increase in the carbon-dioxide combining power as the clinical condition improved: 38 during the acute stage, 41 during beginning convalescence and 58 on recovery.

In 22 cases of *uremia, uremia with cerebral hemorrhage* and *cardiorenal disease*, taking the lowermost fluid, the average for cardiorenal cases was 43.5 (range 22 to 54); for uremia, 43.5 (range 33 to 65); uremia with cerebral hemorrhage, 43.7 (range 6 to 63); and for cerebral hemorrhage alone, 45.4 (range 24 to 55). In a case of uremia with cerebral hemorrhage, fluid taken in successive parts gave 46 for the lowest, then 32–32–34, a variation of 14 volumes per cent. A cistern puncture in a case of cerebral hemorrhage gave 30 for the first fluid removed, and 6 for the final portion. In both of the cases, there was a reduction in the alkali reserve in the uppermost portions of the cerebrospinal fluid. A cistern puncture in another case of cerebral hemorrhage gave a fluid of 45 volumes per cent.

In 3 cases of *tetanus* studied, the range in the lowermost fluids was 50–52–53, the fluid being taken during the stage of acute manifestations.

The range in 5 cases of *cerebrospinal lues* was 43–44–46–31–52, with an average of 47.2. In 2 cases, where successive levels were studied, the figures were 52 for the lower level and 66 for a higher level in 1 case and 44–43–49 for successive levels in another case. Both showed a higher alkaline reserve in the higher fluid, differing from cerebral hemorrhage in this respect. Two cases of luetic meningitis gave 30 and 56 respectively. In paresis, the range was 1–47–50–51–52, the average reading being 50. In tabes, the range was 16 (taboparesis), 46 (taboparesis) 47–53–56–60, with an average of 52.4 (46.3, including the lowest reading).

In *meningococcus meningitis*, the average was 39; *tuberculous meningitis*, 41.35 (range 11 to 52 in 14 fluids); *streptococcus meningitis*, 23–32–32–20; *meningismus* in pneumonia, 39; *leptomeningitis* (cerebral abscess), 33–37–48. In tuberculous meningitis (miliary tuberculous) fluids from successive levels, starting with the lowermost, showed CO_2 combining powers of 32, 35, 36, 35 and 37, 38, 37, 32. Fluids taken at separate intervals during the course of the disease showed in one case 50–48–47–11, in another 46–49–42–46–44, and a third 32–37. Another case of miliary tuberculosis, without meningeal symptoms, was 36. Pulmonary tuberculosis, 40–56.

Four cases of *acute alcoholism* showed 36–43–48–52, with an average of 44.74.

Some observations on *acute poisonings* were: Carbon monoxide, 56; arsenobenzol, 28–36; morphinism, 45–46; hyoscine-morphine, 61 (alkalies intravenously); veronal, 55; impure whiskey, 38–38; methyl alcohol, 48.

In 3 cases of *epilepsy*, the average was 44.6 (37–46–46–46–48). Observations upon fluid from three levels showed the same reading (46). Two cases of skull fracture showed 50–45; in the latter, fluid showed 40–39–43 volumes per cent of combined carbon dioxide.

In 2 cases of *hysteria*, the percentages were 42 and 49. A case

of *melancholia* was 38 and one of *paranoia*, 46. *Senile dementia*, 3 cases, 52–53–56. *Manic depressive insanity* (manic stage), 46. *Typhoid fever*, 39–34. In the latter case, the number was the same at a higher level.

Observations in some other conditions were: *Carcinoma of colon*, 48; *carcinoma of stomach*, 52; *acute pleurisy*, 52; *pharyngeal abscess*, 52; *frontal sinusitis*, 55; *abortion*, 46; *hemorrhagic septicemia*, 28; and in 2 children, *ileocolitis with convulsions*, 36; *encephalitis*, 44.

In successive determinations, there was apparently no relation between the prognosis and the increase or decrease in the alkali reserve of the spinal fluid. The reaction often differed in fluids a few cubic centimeters removed from each other, and the alkali reserve varied as much as 14 points in 5 cc fractions. The range of maximum variations in various fractions was from 0 to 24 volumes per cent. Some cases were mentally clear with variations as much as 14 volumes per cent (F 8215, C. S., lues, 14 volumes per cent; F 8885, C. S., lues, 6), whereas others were hazy, or comatose with variations from 0 to 24 (F 8637, typhoid, 0; F 8823, tuberculous meningitis, 2; F 8853, encephalitis lethargica, 5–1; F 9151, uremia, 14; F 9470, cerebral hemorrhage, 24; F 9732, skull fracture, 6; F 9918 miliary tuberculosis, 0; G 2896, miliary tuberculosis, 10; G 3031, miliary tuberculosis, 4–6).

The foregoing data show that the alkali reserve (carbon-dioxide combining power) of the cerebrospinal fluid may vary at different levels, and the hydrogen-ion concentration may differ. The processes, both mechanical and electrical, which would tend to bring about chemical equilibrium, may have some effect upon the clinical state of the person, but so far no correlation can be made. The circulation must be comparatively slow, and no real comparison with other factors can be made unless fluids from all levels, especially around the brain (ventricles) itself, can be studied The data show no correlation between the plasma-alkali reserve and that of the fluid from a given level. This is probably because the proper venous blood cannot be selected—the difference in composition, in this respect, between the blood from an arm vein and that in the vertebral canal veins may be marked. McClendon[1] noted the alkali reserve to be about 10 per cent lower in the spinal fluid than in the plasma, the alkali reserve, CO_2 tension and hydrogen-ion concentration of blood plasma and spinal fluid in the same person being otherwise the same. Meier[2] considered the CO_2 tension the same or somewhat lower than in the blood. The CO_2 capacity curve was smaller and less buffered than in the serum. Tabes and tuberculous meningitis had no effect upon the reaction or CO_2 capacity The reserve was decreased in 1 case of epidemic meningitis. Tashiro and Levinson[3] suggest the presence of another acid besides carbonic in epidemic meningitis, while carbonic is the acid in tuberculous meningitis. Egerer-Seham and

Nixon[4] reported an average of 53.1 for normals (range, 46.5 to 61.7), decreased in narcolepsy (28.15), pyelonephrosis (23.75), diabetes (22.28) and acidosis (13.6). Tokuoka and Ogasawara[5] noted 63 volumes per cent for spinal fluid in healthy women, with 54.4 volumes per cent for the blood. They noted a decrease after starvation, and in cancer (3 volumes per cent less in spinal fluid and 4.7 volumes per cent less in the blood). Macleod[6] states that "There is as large a percentage of bicarbonate in the cerebrospinal fluid as in the blood plasma. The so-called alkaline reserve, as determined by the Van Slyke method is, therefore, the same as in blood plasma (viz, about 50)."

Nagasawa[7] reports that the combined H_2CO_3 increases with the severity of the symptoms in epidemic meningitis, associated with the increase in polymorphonuclear cells. Bacterial growth increased the combined carbon dioxide, irrespective of that of the blood. Collip and Backus[8] considered that the CO_2 combining power of the plasma is an approximate index of the alkali reserve of the body fluids. The present results, however, suggest that this does not hold under all conditions. In all their human cases, the plasma alkali reserve was higher than that of the spinal fluid.

The variations in composition of the cerebrospinal fluid at different levels has been noted by various workers. Weigeldt[9] and others noted the variation in cell count at different levels, and Ayer and Foster[10] noted the diagnostic significance of differences in the protein content of cistern and lumbar sac fluid. The present work points out that besides the variation in cell count there may also be a variation in reaction and alkali reserve at different levels.

In the data given the curves of distribution of the frequency of cases when plotted in graphic form show a gross similarity between those with no central nervous system symptoms, those with normal globulin and those with normal pressure. The pathological conditions show greater limits of dispersion than the normals. The greatest frequency of the normals lies between 50 and 58 (52 to 54), while in the pathological conditions, the number lies between 40 and 50 (46) for the lowest fraction of the fluid.

Summary and Conclusion. 1. There is no direct correspondence between the carbon-dioxide combining power of the cerebrospinal fluid and the type of disease.

2. A difference in CO_2 combining power was noted in many fluids at different levels around the brain and cord, variations being from 0 to 24 volumes per cent.

3. The average carbon-dioxide combining power of the spinal fluid (lowest fraction) in the absence of nervous symptoms was 50.7 volumes per cent, and was about the same as the average of that of the venous blood taken from the arm, although this was not necessarily true of the individual case.

4. This ratio varied greatly in the presence of symptoms rather

than in diseases as a whole, the spinal fluid number being equal, greater or less than the blood plasma.

5. The average carbon-dioxide combining power of the spinal fluid (lowest fraction) for patients with headaches, was 38.9; unconscious patients, 39.5; stuporous, semicomatose, hazy, drowsy, 41.58; delirium, mania, 41.66; convulsions, 43.37. The ranges for these symptoms, however, covered wide limits.

6. Average for negative Wassermann spinal fluids (lowest fraction), 49.1 volumes per cent; positive Wassermann spinal fluids (lowest fraction), 44.3 volumes per cent.

7. Average for negative globulin (lowest fraction), 45.87 volumes per cent; positive globulin, (lowest fraction), 41.14 volumes per cent.

8. Average for normal pressure (lowest fraction), 49.36 volumes per cent; increased pressure (lowest fraction), 42 volumes per cent.

9. Average for normal cell count (lowest fraction), 48.5 volumes per cent; 8 (and above) cells (lowest fraction), 43.1 volumes per cent.

10. A difference in reaction was noted at different levels.

11. No parallelism was noted between the reaction of the fluid and the alkali reserve.

12. There appeared to be no relation between increase or decrease in the alkali reserve as the case progressed and the prognosis.

13. The carbon-dioxide combining power varied within greater limits in the pathological than in the normal conditions.

14. The greatest frequency of the normal conditions was between 50 and 58 (52 to 54), and in the pathological conditions between 40 and 50 (46) for the lowest fraction.

REFERENCES.

1. McClendon, J. F.: The Formation and Composition of the Cerebrospinal Fluid, Jour. Am. Med. Assn., 1918, **70**, 777.

2. Meier, Klothilde: The Actual Reaction of the Cerebrospinal Fluid, Biochem. Ztschr. ,1921, **124**, 137; Chemical Abstracts, 1922, **16**, 954.

3. Tashiro, S., and Levinson, A.: Alkaloidal and Metallic Precipitation of Cerebrospinal Fluid in the Diagnosis of Meningitis, Jour. Infect. Dis., 1917, **21**, 571.

4. Egerer-Scham, G., and Nixon, C. E.: Comparative Studies in the Chemistry of the Blood and Cerebrospinal Fluid, Arch. Int. Med., 1921, **28**, 561.

5. Tokuoka, E., and Ogasawara, K.: Japan Med. World, December, 1921, p. 16; Chemical Abstracts, 1922, **16**, 1809.

6. Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, 1920, 3d ed., p. 122.

7. Nagasawa, S.: III. The Influence of Polynuclear Leukocytes on the Combined Carbonic Acid Content of the Cerebrospinal Fluid; IV. The Influence of Bacteria on the Combined Carbonic Acid Content of the Cerebrospinal Fluid; V. The Influence of Bacterial Toxins on the Combined Carbonic Acid Content of the Cerebrospinal Fluid, Japan Med. World, January 20, 1922, p. 1, *et seq.*

8. Collip, J. B., and Backus, P. L.: The Alkali Reserve of Blood Plasma, Spinal Fluid and Lymph, Am. Jour. Physiol., 1920, **51**, 551.

9. Weigeldt, W.: Regelmässige Unterschiede in der Zusammensetzung des Liquors an verschiedenen Stellen des subarachnoidealen Raumes, München. med. Wchnschr., 1921, **58**, 838.

10. Ayer, J. B., and Foster, H. E.: Quantitative Estimation of the Total Protein in the Cerebrospinal Fluid, Jour. Am. Med. Assn., 1921, **77**, 366.

BUFFER SOLUTIONS IN INTESTINAL DISEASES.

By Joseph S. Hepburn, Ph.D.,

and

H. M. Eberhard, M.D.

constantine hering research laboratory, hahnemann medical college of philadelphia.

Feces from a healthy person on a properly balanced diet should be either neutral, slightly alkaline or slightly acid in reaction. When carbohydrates are taken in excess, acidity is the rule. If the protein intake is excessive, the stool is likely to be alkaline.

Various pathological conditions and bacterial infections influence the reaction of the feces. Infection with Bacillus fecalis alkaligines gives rise to a decidedly alkaline reaction. Infection with Bacillus aërogenes capsulatus, or with Gram-positive, single or double cocci, frequently produces a highly acid stool.

In chronic excessive saccharobutyric infections in babies, the buttocks and anus frequently become highly irritated as a result of the acid movements. While on the Boston Floating Hospital a number of years ago, one of us (Eberhard) watched with Dr. Arthur I. Kendall many cases of Bacillus aërogenes capsulatus infection, in which the buttocks of the babies were so severely excoriated as a result of the marked fecal acidity that mothers made more comment about the skin condition than the diarrhea.

The gastroenterologist learns by experience that chronic saccharobutyric infections are decidedly more common than the average internist realizes. These infections often mimic such conditions as gastric and duodenal ulcers, gall-bladder diseases, etc., so that operations have been performed in error. Too much credit cannot be given to Herter, Bassler and Kendall for their painstaking researches in intestinal bacteriology and the clinical interpretation of the infections.

The purpose of this paper, is not to give a detailed description of chronic saccharobutyric infection and its treatment, but to report concerning the use of buffer solutions in overcoming the high acidity which is incident to the infection. However, a brief summary of the symptoms and laboratory findings may be helpful. The condition is most frequently caused by Bacillus aërogenes capsulatus, also known as the gas bacillus or Welch bacillus. This is a Gram-positive spore-former, normally present in the intestine in small numbers; it produces gas and gives rise to a marked odor of butyric acid when sown in sterile milk. This odor of rancid butter is characteristic of the feces of patients with this infection. The cultures from the feces may also reveal the presence of Bacillus putrificus, the bacillus of malignant edema, and Gram-positive

coccal forms. One of the characteristics of the feces, directly examined on a slide, is the marked preponderance of all Gram-positive organisms. Among the symptoms is diarrhea preceded by a crampy pain in the abdomen; it alternates with periods of normal defecation. During these periods the symptoms may be simply marked or slight crampy pains throughout the abdomen. This pain, like the diarrhea, is made worse by sugars; in fact, by all carbohydrates. Unlike gastric ulcer, neither food nor alkali affords relief. A brisk purge relieves the diarrhea and the pain for only a short time. The feces are characteristic; they have a very light yellow color, doubtless due to the presence of a large amount of hydrogen in the bowel and its reducing action on the bile pigments. Patients frequently comment on the marked odor of rancid butter, due to the presence of butyric acid. The feces usually are markedly acid on account of the presence of propionic, butyric, valeric and caproic acids. Macroscopically, they are foamy and contain much mucus; occasionally blood is visible; a low specific gravity is common. Much gas is formed, as a rule, when the feces are incubated in Bauermeister or other fermentation tubes. Microscopically, many degenerated cells are found, perhaps as a result of the irritant action of certain products of the fermentation. Apthae in the mouth are common, especially after partaking of sweets such as candy and ice-cream. One of us (Eberhard), has frequently found traces of occult blood in the gastric contents and feces of these patients; this lends support to the theory that such infection might be the cause of ulcers in the alimentary canal. Neurasthenic symptoms are common, anxiety, depression, etc. Belching of gas and acid risings are also common due, no doubt, to an increased gradient in the ileum and the upper colon. The treatment, generally, is a high protein diet for a time, not continued too long, however, since the organisms early become facultative. Others forms of treatment are transintestinal lavage with hypertonic salt solution, rectal implantation of Bacillus coli, cultured from the patient's own feces, irrigation with alkalies, etc.

While treating patients with such infection they too often become restive on account of frequent relapses. Even with the best forms of treatment, recurrences in the face of progress are common. Patients are annoyed with the pain and excoriation of the buttocks and demand some form of relief. Most clinicians prescribe colon irrigation of sodium bicarbonate which at least gives some comfort for a while. At times, however, the carbon dioxide gas generated from the bicarbonate is more annoying than the pain and diarrhea.

We have noted one alarming case of cardiac embarrassment due to the gas. Moreover, the sudden generation of gas may cause a rupture of an ulcerated bowel.

In order to neutralize the intestinal contents, without the pro-

duction of gas, we have applied buffer solutions in the treatment of these infections. The solutions are administered by rectal injection. The results have been extremely encouraging, as may be seen from the typical cases reported below.

Clark[1] defines a buffer solution as a solution which is able to resist change in its hydrogen-ion concentration by addition or loss of acid or alkali. Such solutions usually contain two compounds. Take, for instance, a solution containing both a primary and a secondary phosphate: Such a solution can combine with fairly large amounts of either acid or alkali. Acids cannot impart to it a reaction more acid than that of phosphoric acid until all the phosphates have been decomposed. Alkalies cannot impart to it a reaction more alkaline than that of trisodium phosphate until all the phosphates have been converted into that salt.

In the treatment of intestinal acidity, it has been necessary to use buffer solutions which could not possibly liberate gases within the intestine, while neutralizing its acid contents; therefore, bicarbonates could not be used. Recourse has been had to two buffer solutions, which may be designated as the phosphate buffer solution and the citrate buffer solution. Both solutions were made according to the directions of Sörensen[2] immediately prior to use. If the solutions be kept for some time, they may become infected by moulds; this is especially true of the citrate buffer solution.

The phosphate buffer solution had a hydrogen-ion concentration P_H of 8.043; it was prepared by mixing a $\frac{1}{15}$ molar solution of primary potassium phosphate and a $\frac{1}{15}$ molar solution of secondary sodium phosphate in the ratio of 0.5 mil of the former to 9.5 mils of the latter.

The citrate buffer solution had a hydrogen-ion concentration P_H of 12.364; it was prepared by mixing a $\frac{1}{10}$ molar solution of secondary sodium citrate, and an exactly $\frac{1}{10}$ normal solution of carbonate-free sodium hydroxide in the ratio of 4 mils of the former to 6 mils of the latter.

Of the two buffers, the citrate solution was used more frequently, since it possessed a greater alkali reserve; that is, had a lower hydrogen-ion concentration and a higher hydroxyl-ion concentration, and, therefore, was able to neutralize more acid before its reaction was reduced to that of normal feces which have a hydrogen-ion concentration P_H between 7.0 and 7.5 according to Robinson.[3]

A résumé is given of three typical cases:

Case I.—Mr. A. Enterocolitis for ten years. Six to eight movements daily of a very light yellow stool. Marked tenesmus. Great amount of flatus. Eczema of anus and buttocks. Frequent attacks of colic, followed by diarrhea. Gastric analysis showed a marked hypersecretion of the fasting stomach, (120 mils); free hydrochloric acid, 60; total acidity, 80. A fractional test breakfast

of 250 mils of tea and 50 grams of bread showed the highest peak of free hydrochloric acid at the second hour. Motor end point at three hours. Roentgen ray revealed a normal stomach, with atony. Feces: Excessively acid, great excess of all Gram-positive organisms; culture yielded Bacillus aërogenes capsulatus and many single and double cocci. Gas unusually abundant in Bauermeister fermentation tube. After diet and other treatment failed to reduce the acidity and diarrhea, 1 liter of the phosphate buffer solution was injected per rectum. The next movement was neutral in reaction, the number of movements never exceeded two daily. Above all, the colic, which had persisted for years, was relieved. Frequent injections of the buffer solution controlled the remaining symptoms. The eczema disappeared in a surprisingly short period of time.

Case II.—Mrs. C., aged thirty years. For two years has had "sore tongue," an examination of which showed marked redness of the dorsum and two small ulcers on the tip. Patient states the condition disappears for a week, or more, then returns. At times, small ulcers also develop near the frenum of the tongue. No gastrointestinal symptoms, excepting a persistent pain in the epigastrium; not relieved by food, alkali nor lavage. Wassermann reaction negative with both blood and spinal fluid. Roentgen ray examination of gastrointestinal canal, negative. Gastric analysis: 110 mils of gastric contents after a twelve-hour fast; fractional analysis showed decided hyperacidity; highest peak at one hour after tea and toast; motor end point at two and one-half hours. Feces: Marked preponderance of all Gram-positive organisms. After a Bassler modification of the Schmidt and Strassburger test diet, light yellow feces with a marked acid reaction and a pronounced odor of butyric acid, containing reduced bile pigments, according to the mercuric chloride (sublimate) test, and showing a decided increase of all Gram-positive organisms; no occult blood; excessive gas on incubation in Bauermeister tubes. Treatment: High protein diet, transintestinal lavage, etc., gave no relief; the ulcers near the frenum and the soreness of the tongue continued; the stool remained markedly acid in reaction. Two high colon injections of the citrate buffer solution produced an alkaline stool with no return of the tongue or mouth condition.

Case III.—Male, aged forty years. History of persistent general abdominal pain for ten years. Five years ago had appendix removed and gall-bladder drained for three weeks by cholecystotomy; much improvement was experienced for three months, then the general indefinite pain returned. Examination showed a well-nourished man; teeth and tonsils in good condition; chest negative; maximum systolic pressure, 128/82; reflexes normal;

abdominal habitus normal; many diffuse tender points, especially along the colon. Sigmoidoscope examination of the rectum showed marked general inflammation with tendency toward spasm. Gastric analysis revealed 120 mils of contents in the fasting stomach. Free hydrochloric acid was 62; total acidity, 96. An Ewald test breakfast of 250 mils plain tea and 50 grams toast showed the motor end point at three and one-half hours. The highest values for both free hydrochloric acid and total acidity occurred at two hours. Occult blood was absent. A culture was made of the contents of the fasting duodenum including bile, obtained after the administration of a 25 per cent solution of magnesium sulphate; Bacillus coli was found in the culture. Feces: Were strongly acid, contained much adherent mucus and had a decided odor of butyric acid; fatty acids were extremely abundant. Bacillus aërogenes capsulatus and many single cocci preponderated in the bacterial flora. A count showed 86 Gram-positive to 14 Gram-negative organisms. In fermentation tubes, gas and acid were formed in excessive amounts. The patient had a diarrhea, five or six movements daily, very acrid, and causing much tenesmus. Colic was so severe that morphine had to be given from time to time. A small amount of food produced immediate distress, and retention vomiting was common. A Roentgen ray study revealed only a mild pylorospasm. The patient had been advised to have another operation.

Duodenal lavage twice weekly with drainage of the bile tracts by administration of a 25 per cent solution of magnesium sulphate, rest in bed, Bacillus coli vaccine and a high protein diet relieved all the symptoms but the acid stool and tenesmus. These symptoms were relieved by three treatments with the citrate buffer solution at semiweekly intervals, administering 1 liter of the solution by rectum at each treatment. One month after the last injection of buffer solution, the gastric motility was normal, and the ratio of Gram-positive to Gram-negative organisms was 40:60. The drainage of bile, high protein diet, and vaccine reduced the colon gradient and relieved the pylorospasm, while the buffer solution relieved the acid stool and tenesmus. This patient will probably require a number of injections of the buffer solution, and will have to maintain a high protein intake in order to keep in control the Gram-negative organisms. The buffer solution can at least be depended upon for relief.

These cases are examples of what has been accomplished by rectal injection of buffer solutions. Many cases have been treated; and a number are still under observation. While we do not claim curative results nor anything revolutionary, yet, we think that buffer solutions are worthy of trial for the relief of distressing colic and for the securing of bowel neutrality.

Summary. Clinically, we have noted a marked improvement in subjective and objective symptoms of intestinal disease with the use of buffers. The ratio between Gram-negative and Gram-positive organisms was reëstablished very frequently after the first or second enema. We feel that while the use of a buffer solution is still experimental, enough evidence has been gathered to indicate its use and to show its value.

REFERENCES.

1. Clark: The Determination of Hydrogen-ions, Williams & Wilkins Co., Baltimore, 1920, p. 31.
2. Sörensen: Ergebn. d. Physiol., 1912, **12**, 393.
3. Robinson: Jour. of Biol. Chem., 1922, **52**, 445.

CREATININEMIA: BASED UPON A STUDY OF FIFTEEN HUNDRED BLOOD CHEMICAL ANALYSES.

By Henry M. Feinblatt, M.D.,
BROOKLYN, N. Y.

(From the Clinical Laboratory, Department of Internal Medicine, Long Island College Hospital, Brooklyn, N. Y.)

The introduction of clinical methods for blood chemical analyses gave a great impetus to the study of the nephropathies. So great is the reliance placed upon these findings that a blood chemistry examination is commonly demanded in every case of renal disease. Diagnosis, prognosis and treatment are influenced to a considerable degree by the results of these tests.

The significance of the retention of non-protein nitrogen and of its principal components, urea, uric acid and creatinin, has many times been clearly stated. However, a review of the literature discloses the fact that, in the case of creatinin, the conclusions, considering their importance, have been based upon rather small groups of cases. In respect to creatinin, attention has so largely been focussed upon its retention in nephritis that it appeared desirable to study a large consecutive series in order to ascertain whether that condition may be present in other states. The almost routine use of blood chemical analyses on the Medical Service of the Long Island College Hospital offered an excellent opportunity for collecting and analyzing such a group. It was felt that the analysis of these 1500 cases, while, perhaps, not modifying conclusions already reached, would be of value by adding such confirmation to present views as only a large series can give.

TABLE I.

Case.	Age.	Sex.	Blood chemistry. Date.	No. of days before death.	Mgs. per 100 cc. Creatinin.	Urea N.	Uric acid.	Sugar.	Date of discharge or death.	Result.	Diagnosis.	Complications and remarks.
1. A. G.	46	F.	May 17, 1920	6	20.0	300.0	10.00	196.0	May 23, 1920	Died	Chronic glomerulonephritis	Semicomatose and delirious.
			22, 1920	1	30.0	300.0	...	285.0				
2. J. S.	33	F.	24, 1920	1	28.0	300.0	50.00	240.8	25, 1920	Died	Chronic glomerulonephritis	Uremia.
3. M. V.	24	M.	April 1, 1920	6	15.0	200.0	20.00	181.8	April 7, 1920	Died	Acute diffuse glomerulonephritis	Uremia.
			6, 1920	1	20.0	300.0	...	235.2				
4. E. C.	75	F.	June 13, 1920	0	20.0	300.0	15.50	333.3	June 13, 1920	Died	Chronic glomerulonephritis	Uremia.
5. V. H.	25	M.	Feb. 17, 1920	11	7.5	50.0	6.20	133.3	Feb. 28, 1920	Died	Acute exacerbation of chronic glomerulonephritis	Uremia.
			21, 1920	7	8.6	300.0	12.50	200.0				
			24, 1920	4	15.0	300.0	8.20	143.0				
			27, 1920	1	20.0	375.0	5.00	138.0				
6. C. J.	39	M.	June 22, 1920	0	15.0	375.0	35.70	86.0	June 22, 1920	Died	Chronic glomerulonephritis	Uremia, pulmonary tuberculosis, amyloid kidneys and spleen; necropsy showed pulmonary tuberculosis amyloid kidneys and spleen.
7. W. D.	27	M.	May 28, 1920	7	15.0	130.4	8.80	200.0	June 4, 1920	Died	Chronic glomerulonephritis	Uremia.
			June 1, 1920	3	15.0	50.0	33.30	153.8				
8. R. M.	25	M.	Feb. 20, 1921	0	15.0	150.0	10.00	142.0	Feb. 20, 1921	Died	Chronic glomerulonephritis	Uremia; diagnosis confirmed at necropsy.
9. J. S.	28	M.	Oct. 27, 1921	10	15.0	60.0	6.25	181.0	Nov. 6, 1921	Died	Chronic glomerulonephritis	Uremia.
			Nov. 1, 1921	5	14.0	75.0	10.25	136.0				
10. A. C.	25	F.	May 3, 1919	5	8.0	117.6	...	143.0	May 8, 1919	Died	Bichloride poisoning nephrosis with anuria	Took three bichloride tablets, April 28, 1919; necropsy showed coagulation necrosis of kidneys and ulcers in stomach.
			4, 1919	4	10.2	86.8	...	...				
			5, 1919	3	13.3	140.0	...	166.6				
			7, 1919	1	14.8	121.8	14.12	250.0				
11. T. R.	41	M.	Jan. 23, 1920	1	11.0	300.0	25.00	70.0	Feb. 24, 1920	Died	Chronic glomerulonephritis	Uremia.
12. R. V.	23	F.	Oct. 20, 1919	17	6.7	60.0	11.10	80.0	Nov. 6, 1920	Died	Nephrectomy, other kidney being congenitally cystic	Uremia.
			24, 1919	13	10.3	100.0	16.00	110.0				
13. C. K.	66	M.	Nov. 4, 1920	0	10.0	225.0	16.25	125.0	Nov. 4, 1920	Died	Chronic glomerulonephritis	Pleurisy and pericarditis.
14. A. C.	29	M.	Aug. 4, 1921	3	10.0	75.0	25.00	80.0	Aug. 7, 1921	Died	Chronic glomerulonephritis	Uremia; confirmed by necropsy
15. J. C.	28	M.	Dec. 24, 1918	10	3.2	22.40	...	166.6	Jan. 3, 1919	Died	Acute diffuse glomerulonephritis	Lobar pneumonia; confirmed by necropsy.
			31, 1918	3	8.8	26.60	...	166.6				
16. E. C.	35	F.	Nov. 11, 1921	49	8.4	53.0	6.66	153.0	Dec. 30, 1921	Died	Chronic glomerulonephritis	Phenolsulphonephthalein test, 0.
17. A. A.	29	F.	Feb. 17, 1920	6	6.5	100.0	10.00	142.8	Feb. 23, 1920	Died	Bichloride poisoning; nephrosis (coagulation necrosis tubules)	Anuria; uremia.
			18, 1920	5	7.5	200.0						
			19, 1920	4	6.6	115.3	6.30	200.0				
			20, 1920	3	7.3	230.0	12.50					
18. G. N.	21	F.	Nov. 11, 1919	2	7.5	120.0	12.50	200.0	Nov. 13, 1919	Died	Chronic glomerulonephritis	Uremia; perforation of uterus, peritonitis and bacteriemia.
19. L. K.	34	F.	Mar. 12, 1921	2	6.00	100.0	25.00	95.0	Mar. 14, 1921	Died	Chronic glomerulonephritis	Tertiary syphilis; confirmed by necropsy.
			14, 1921	0	6.75	125.0	25.00	111.0				
20. S. L.	55	F.	Sept. 29, 1921	0	6.75	150.0	25.00	105.0	Sept. 29, 1921	Died	Chronic glomerulonephritis	Uremia; confirmed by necropsy.
21. W. G.	58	M.	Oct. 27, 1919	7	6.50	88.2	5.00	133.3	Nov. 3, 1919	Died	Chronic glomerulonephritis	General paresis; uremia.
			31, 1919	3	5.00	150.0	5.50	110.0				
22. M. C.	48	M.	Aug. 10, 1920	...	6.00	75.0	5.00	115.0	Sept. 8, 1920	Improved	Mixed type, chronic glomerulonephritis plus nephrosis	Cardiac incompetence; limited fluid intake and digitalis yielded marked improvement.
			14, 1920	...	6.00	75.0	12.50	99.0				
			25, 1920	...	4.90	99.0	6.00	133.0				
			Sept. 2, 1920	...	3.90	37.5	4.20	133.0				

22. M. C.	48	M.	31, 1919	3	5.00	150.0	5.50	110.0	Nov. 3, 1919	Died	Chronic glomerulonephritis	General paresis; uremia.
			Aug. 10, 1920		6.00	75.0	5.00	115.0	Sept. 8, 1920	Improved	Mixed type, chronic glomerulonephritis plus nephrosis	Cardiac incompetence; limited fluid intake and digitalis yielded marked improvement.
			14, 1920		6.00	75.0	12.50	91.0				
			25, 1920		4.90	60.0	6.00	133.0				
			Sept. 2, 1920		3.00	37.5	4.20	133.0				
23. A. I.	57	M.	Aug. 28, 1920	10	2.25	150.0	7.10	250.0	Sept. 7, 1920	Died	Chronic glomerulonephritis	Uremia.
			Sept. 4, 1920	5	0.00	300.0	10.00	285.0				
24. R. M.	24	M.	Oct. 9, 1920	337	2.40	60.0	5.00	220.0	Aug. 12, 1921	Died	Chronic glomerulonephritis	Arteriosclerosis; uremia.
			18, 1920	398	6.00	100.0	10.00	166.0				
			22, 1920	294	5.00	60.0	8.33	100.0				
25. D. S.	43	M.	Oct. 27, 1921	28	2.84	37.5	7.13	83.0	Nov. 24, 1921	Died	Chronic glomerulonephritis	Confirmed by necropsy.
			Nov. 1, 1921	23	2.16	55.0	9.17	71.0				
			11, 1921	13	5.80	48.5	12.50	133.0				
			18, 1921	6	5.00	60.0	14.40	111.0				
26. S. W.	46	F.	Oct. 20, 1920	174	5.00	33.8	10.00	100.0	April 12, 1921	Died	Chronic glomerulonephritis	Cerebral hemorrhage; myocardial insufficiency; twice discharged in improved condition; died a cardiac death.
			25, 1920	169	2.00	18.8	5.55	118.0				
			Nov. 10, 1920	153	3.75	18.8	7.13	111.0				
			22, 1920	141	2.13	16.7	5.55	111.0				
			Dec. 31, 1920	102	1.36	42.8	3.70	153.0				
			Jan. 6, 1921	96	1.50	30.0	3.13	125.0				
			13, 1921	89	1.36	14.3	4.15	100.0				
			26, 1921	76	1.67	12.0	2.63	83.0				
			Mar. 15, 1921	28	1.50	42.8	2.84	166.0				
			22, 1921	21	1.57	42.8	6.25	181.0				
			31, 1921	12	1.50	37.5	3.33	100.0				
			April 6, 1921	6	2.13	24.9	4.15	400.0				
27. H. G.	43	F.	Mar. 26, 1921	10	3.75	50.0	8.33	166.0	April 5, 1921	Died	Acute exacerbation of chronic glomerulonephritis	Confirmed by necropsy.
			29, 1921	7	4.28	60.0	4.15	111.0				
28. M. A.	21	F.	Jan. 3, 1921	86	4.28	100.0	8.33	142.0	Mar. 30, 1920	Died	Chronic glomerulonephritis	Albuminuric retinitis; phenolsulphonephthalein test, 20 per cent.
			6, 1921	83	3.33	60.0	5.55	118.0				
			14, 1921	75	2.49	21.3	5.00	80.0				
29. B. R.	35	M.	Aug. 3, 1921	..	3.75	80.3	16.25	74.0	Aug. 13, 1921	Improved	Chronic glomerulonephritis	Lead poisoning.
			12, 1921	..	1.50	20.0	3.55	133.0				
30. J. M.	47	M.	Jan. 15, 1920	13	3.00	100.0	8.00	118.0	Jan. 28, 1920	Died	Chronic glomerulonephritis	Uremia.
			21, 1920	7	3.00	103.0	8.90	143.0				
			24, 1920	4	3.60	150.0	14.30	125.0				
31. H. W.	43	M.	Mar. 30, 1921	5	1.67	42.8	5.00	111.0	April 4, 1921	Died	Chronic glomerulonephritis	Uremia; died in coma; aortic regurgitation; confirmed by necropsy.
			April 6, 1921	0	3.33	100.0	16.25	133.0				
32. S. C.	43	F.	Mar. 21, 1919	108	3.17	22.4	...	...	July 7, 1919	Died	Chronic glomerulonephritis	
33. A. C.	60	M.	April 5, 1919	146	3.12	16.66	...	192.3	Aug. 29, 1919	Died	Chronic glomerulonephritis	Myocardial insufficiency.
34. H. L.	66	M.	Mar. 27, 1919	...	3.07	19.6	...	263.0	April 8, 1919	Improved	Chronic glomerulonephritis	Arteriosclerosis; cerebral angiospasm.
35. R. F.	32	F.	Oct. 7, 1921	49	3.00	17.6	5.20	267.5	Nov. 25, 1921	Died	Chronic glomerulonephritis	No glycosuria.
36. M. S.	18	F.	May 3, 1920	?	2.00	20.0	4.20	105.0	Sept. 9, 1920	Died	Chronic glomerulonephritis	Syphilis; date of death unknown.
			10, 1920	?	1.90	15.0	2.00	116.0				
			July 8, 1920	?	1.50	25.0	...	87.0				
			Aug. 13, 1920	?	3.00	60.0	10.00	100.0				
37. C. M.	67	F.	July 13, 1920	?	3.00	30.0	10.00	143.0	July 30, 1920	Died	Chronic glomerulonephritis	Chronic myocarditis; date of death unknown.
38. A. B.	58	M.	June 8, 1920	7	1.50	16.0	3.40	...	June 15, 1920	Died	Chronic glomerulonephritis	Myocardial insufficiency; died of bronchopneumonia.
			15, 1920	0	2.90	83.3	8.30	133.3				
39. F. N.	34	M.	May 12, 1919	7	2.86	39.2	5.04	116.2	May 29, 1919	Died	Chronic glomerulonephritis	Tertiary syphilis; died of bacteriemia.
40. H. W.	63	M.	April 9, 1920	10	2.72	91.6	16.25	...	April 19, 1921	Died	Chronic glomerulonephritis	Prostatic hypertrophy.
41. W. N.	78	M.	Mar. 19, 1919	...	2.70	33.6	...	138.0	Mar. 29, 1919	Improved	Chronic glomerulonephritis	Arteriosclerosis; emphysema; alive May 22, 1922, but unable to work.
42. C. S.	40	M.	Jan. 14, 1919	...	2.60	16.8	...	142.8	Jan. 28, 1919	Improved	Chronic glomerulonephritis	
43. R. H.	42	M.	Sept. 29, 1919	...	2.60	50.0	...	72.0	Oct. 28, 1919	Improved	Chronic glomerulonephritis	Returned to work.
			Oct. 8, 1919	...	2.50	60.0	4.50					

LITERATURE. The pioneer work upon creatinin retention was done by Folin and Denis.[1] There had been but few previous determinations of this substance in the blood. Earlier researches had centered around the estimation of creatinin in the urine. Because of its uniform rate of elimination, even on a low-protein diet, and of its relation to creatin, it furnished a valuable index to the level of tissue metabolism. Hence, as might be expected, the elimination of creatinin in the urine was found to be increased in febrile states and in exophthalmic goiter.

Physiological data upon creatinin and its role in the metabolic processes foreshadowed its eventual clinical importance. Of all the non-protein nitrogenous products it is the one least influenced by dietary factors. It is believed to be derived exclusively from the creatin contained in all tissues, of which substance it is the anhydrid. Placing an individual upon a meat-free diet does not materially diminish the creatinin excretion. However, the ingestion of large doses (20 gm.) of creatinin had been shown by Rose and Dimmitt[2] to lead to a perceptible increase (0.49 gm.) in the output of creatinin.

Because of the fact that the kidneys eliminate creatinin with especial ease, its blood concentration (1 to 2 mg. per 100 cc) remains remarkably constant. This fact suggested the employment of a clinical method for the determination of the blood creatinin.

Folin and Denis[1] measured the creatinin in the blood of 200 hospital patients with non-renal conditions and found no retention in them. On the other hand, accumulation of creatinin was noted in uremia and terminal nephritis, and high figures appeared to portend early death.

Myers and Lough[3] confirmed these findings. Their conclusions were that a creatinin figure of from 2.5 to 3 is suspicious; that a reading of from 3 to 5 indicates severe renal damage and that figures over 5 foreshadow a fatal termination within two months.

In 1916, Chace and Myers[4] formulated their views upon the clinical importance of creatinin in the following words: "As a prognostic test the blood creatinin has been found of very great service, over 5 mg. to 100 cc having invariably proved fatal after the lapse of a comparatively short period of time. During the terminal stages of the disease, the concentration of the creatinin gradually rises, reaching 15 to 30 mg. in most cases at death."

In 1918, Myers and Killian[5] reaffirmed the same views.

For a time, serious doubt was cast upon the whole question of creatininemia, when McCrudden and Sargent,[6] in 1916, announced that all of the variations in the colorimetric readings could be accounted for by slight differences in the amount of picric acid contained in the solution. They stated that the color due to the creatinin contributed but a small portion of the total hue. As the Folin colorimetric method had been the one employed in the

clinical determinations, this indictment, if true, would have completely nullified all previous work on creatinin retention. Folin and Doisy[7] immediately reinvestigated the whole subject. Together with McCrudden and Sargent, they examined the latters' picric acid and found it to be surprisingly impure. Pure picric acid gives only a faint tinge to the solution.

Since that time the literature upon the subject has not been voluminous, and there has been no serious contradiction to the conception originally promulgated by Folin and Denis. Rabinowitch,[8] in 1921, emphasized the prognostic value, reporting 14 cases with creatinin figures over 5, all of which were necropsied and showed marked renal damage.

The general rule that laboratory findings must be correlated with the clinical data in order to be properly interpreted allows no exception in the case of creatinin. If the retention be of sudden onset and due to a remediable cause, such as ureteral calculus or hypertrophied prostate, prompt recovery may be expected upon removal of the defect. This fact is brilliantly illustrated by the experiments of Keith and Pulford.[9] These investigators produced hydronephrosis in dogs by ligating the ureters with a rubber band. When the obstruction was maintained for too long a time, permanent kidney damage was done and the animals died; but when the obstruction was removed in time, even though the blood creatinin had already reached abnormally high values, complete recovery took place.

Technic. The technic originally described by Folin and Denis still occupies first place. Modifications subsequently suggested have added nothing to it. It was the method employed in this series of blood analyses. The details of the test are contained in an article by Folin and Wu.[10]

Material Studied. Out of 1500 routine blood chemical analyses taken in the wards of the Long Island College Hospital, there were selected all of those cases, regardless of diagnosis, which exhibited a blood creatinin figure in excess of 2.5 mg. per 100 cc. The routine use of these analyses should be stressed. Only a small percentage of the whole group of individuals was suffering from renal disease. The data upon all of the creatininemic patients are tabulated in Table I. The relation between the date of the blood chemical analysis and that of death should be particularly noted, inasmuch as the creatinin determination is so commonly used as a prognostic guide. The patients showing retention were followed up after their discharge from the hospital, and every effort was made to determine the exact date of death.

Analysis of Table I. Forty-three cases showed at some period a blood creatinin value in excess of 2.5. Table II, below, shows that every one of these patients gave evidence of renal damage.

TABLE II.—SUMMARY OF CLINICAL DIAGNOSES IN ALL CASES SHOWING CREATININEMIA.

Chronic diffuse glomerulonephritis	35
Acute exacerbation of chronic glomerulonephritis	2
Acute diffuse glomerulonephritis	2
Bichloride poisoning, nephrosis with anuria	2
Mixed type, chronic glomerulonephritis plus nephrosis	1
Nephrectomy, other kidney being congenitally cystic	1

These findings are quite in accord with the accepted view. It may, perhaps, appear surprising not to find a single borderline or non-nephritic case out of such a large series. The deduction is safe that creatinin is very easily eliminated by the normal or even the moderately damaged kidney and that creatinin retention is an unmistakable sign of great functional inefficiency. However, it must be borne in mind that anuria, from any cause, whatsoever, is capable of causing a rapidly mounting creatininemia. Reference to Case X, in which there was complete anuria, due to bichloride poisoning, demonstrates how quickly creatinin retention figures may rise in the absence of urinary secretion. It is noteworthy that all of the patients in the retention category, with the exception of the three anuric individuals, gave evidence of lesions of the glomeruli.

Prognostic Inferences. The first 14 cases listed in Table I attained creatinin figures of 10 mg. per 100 cc or more. All of these patients died within less than three weeks. The longest period of survival was seventeen days. The average length of life after reaching this figure was four days.

Fifteen patients yielded readings between 5 and 10 mg. per 100 cc. Eleven of these individuals died uremic within seventeen days, the average being six days. Three others have since died at intervals of two hundred and ninety-eight, one hundred and seventy-four and forty-nine days respectively. Two cases of this group, Nos. XXII and XXVI, deserve especial consideration, as they indicate that recovery may take place even after the creatinin figure has exceeded 5. The former exhibited the block type of retention. The patient was edematous and oliguric, and there was myocardial insufficiency. Treatment with rest, limitation of fluid intake and digitalis resulted in marked improvement with a parallel reduction in the retention figures. He was discharged greatly improved at the end of a month. Case XXVI actually attained normal blood chemical values and was discharged from the hospital in excellent condition. A concurrent cerebral hemorrhage with cardiac decompensation subsequently caused death, but at that time there was but slight retention of creatinin and urea. These 2 cases serve to emphasize the fact that with retention exceeding 5 mg. per 100 cc, the prognosis as regards the renal condition, while grave, is not necessarily hopeless.

TABLE III.—OUTCOME WITH VARIOUS DEGREES OF RETENTION.

Creatinin figure.	Died.	Max. No. of days.	Aver. No. of days.	Unimproved.	Improved.
Over 10 mg.	14	17	4	0	0
5.0 to 10 "	14	298	42	0	1
2.5 to 5 "	16	..	..	0	5

Comparison with Retention of Urea and Uric Acid. It will be observed that the figures for creatinin and for urea appear to rise in a rough ratio; but too much reliance must not be placed upon this relationship. Thus one analysis yielded a reading of 6 mg. of creatinin and 300 mg. of urea nitrogen. In another case, values of 8.8 mg. of creatinin and only 26.6 mg. of urea nitrogen were obtained. There was not a single instance in which creatinin but not urea was retained. In a previous paper upon uremia,[11] studied from the aspect of retention of urea, the fact was pointed out that urea nitrogen furnishes a more delicate guide and gives earlier evidence of renal deficit. In that group of 29 cases, the rough ratio between creatinin and urea nitrogen was likewise apparent.

Accumulation of uric acid bears a very inconstant relation and its readings are of little assistance in forming a prognosis. Together with the other non-protein nitrogen ingredients, its blood values are increased in nephritis, but the figures are so variable that sound inferences cannot be drawn from the level of its retention. Myers, Fine and Lough[12] expressed the belief that uric acid, because of the complexity of its molecule, is eliminated with great difficulty and that, consequently, retention of this substance is an indication of early nephritis. The author[13] has just completed the study of a series of cases with retention of uric acid but of none of the other non-protein nitrogen substances. So far as he has been able to observe, this retention occurs in a great variety of unrelated conditions and is not a reliable index to incipient renal insufficiency.

Summary. Fifteen hundred blood chemical analyses were made upon patients in the wards of the Long Island College Hospital. As it was desired to study creatinin retention in any conditions in which it might possibly occur, there was no selection of cases. The blood values exceeded 2.5 mg. per 100 cc in 43 patients. An analysis of this group showed that in all there were other unmistakable evidences of renal deficit. Forty cases were diagnosed as glomerulonephritis, while the other 3 patients were anuric.

Fourteen patients attained figures of 10 mg. or over per 100 cc. All of these patients died within seventeen days, the average length of life being four days. Of 15 patients who yielded figures from 5 to 10 mg., 11 were dead within seventeen days, averaging six days. Three others have since died. One of the latter finally succumbed to a cerebral hemorrhage after having attained normal blood chemical values. Of 21 patients with readings ranging from 2.5 to 5 mg., 16 are now dead.

REFERENCES.

1. Folin, O., and Denis, W.: On the Creatinine and Creatine Content of Blood, Jour. Biol. Chem., 1914, **17**, 487.
2. Rose, W. C., and Dimmitt, F. W.: Experimental Studies on Creatine and Creatinine (VII. The Fate of Creatine and Creatinine When Administered to Man), Jour. Biol. Chem., 1916, **26**, 345.
3. Myers, V. C., and Lough, W. G.: The Creatinin of the Blood in Nephritis: Its Diagnostic Value, Arch. Int. Med., 1915, **16**, 536.
4. Chace, A. F., and Myers, V. C.: The Value of Recent Laboratory Tests in the Diagnosis and Treatment of Nephritis, Jour. Am. Med. Assn., 1916, **67**, 929.
5. Myers, V. C., and Killian, J. A.: The Prognostic Value of the Creatinin of the Blood in Nephritis, Proc. Soc. Exper. Biol. and Med., 1918, **16**, 41.
6. McCrudden, F. H., and Sargent, C. S.: Influence of Color from Sodium Picrate in Determination of Creatinin in Blood and Urine, Jour. Biol. Chem., 1916, **26**, 527.
7. Folin, O., and Doisy, E. A.: Impure Picric Acid as a Source of Error in Creatine and Creatinine Determinations, Jour. Biol. Chem., 1917, **28**, 349.
8. Rabinowitch, I. M.: The Prognostic Value of the Study of the Blood Creatinine in Nephritis, Canadian Med. Assn. Jour., 1921, **11**, 320.
9. Keith, N. M., and Pulford, D. S.: Experimental Hydronephrosis, Arch. Int. Med., 1917, **20**, 853.
10. Folin, O., and Wu, H.: Jour. Biol. Chem., 1919, **38**, 106.
11. Feinblatt, H. M.: Uremia: An Analysis of Twenty-nine Cases, New York Med. Jour. (in press).
12. Myers, V. C., Fine, M. S., and Lough, W. G.: The Significance of the Uric Acid, Urea and Creatinine of the Blood in Nephritis, Arch. Int. Med., 1916, **17**, 570.
13. Feinblatt, H. M.: Uricacidemia: Based upon a Study of Fifteen Hundred Blood Chemical Analyses Arch. Int. Med., 1923, **31**, 758.

OBSERVATIONS ON THE ACTION OF GERMANIUM DIOXIDE IN PERNICIOUS ANEMIA.

By M. E. Alexander, M.D.,

VISITING PHYSICIAN, WATERBURY HOSPITAL, WATERBURY, CONN.

The experimental work conducted by Hammett, Nowrey and Müller on the erythropoietic action of germanium dioxide[1] suggested to me to make some clinical observation upon the action of this substance in cases of pernicious anemia. The abovenamed investigators showed that the administration of the germanium to albino rats led to "a marked and statistically valid rise in the number of erythrocytes." Their experimental work was suggested by the close relationship existing between the positions of germanium and arsenic in the periodic system, where they are adjacent in series. They also showed that germanium possesses a toxicity approximately twenty-two times less than that of arsenic. They administered subcutaneously to animals 180 mg. of germanium per kilo of body weight with no harmful effects, while arsenic exhibits fatal results at a rate of 8 mg. per kilo of body weight.

Müller and Iszard[2] published observations upon the action of

[1] Jour. Exper. Med., 1922, **19**, 173.
[2] Am. Jour. Med. Sci., 1922, **153**, 364.

germanium dioxide. The work was conducted upon the guinea-pig, rabbit, dog and one apparently normal man. They used a stable, saturated solution containing 0.004684 gm. of germanium dioxide per 1 cc, representing "the true solubility of the pure oxide in water." The lastnamed authors also made elaborate and extremely valuable determinations upon the cumulative effect and elimination of the substance.

The present paper is based upon observations made in 3 cases of pernicious anemia. The accompanying tables indicate the exact blood findings in each case. In my experience the results have been very disappointing and, because of the tremendous expense of this product, it seemed to me wise to report the findings, even though the experience is comparatively limited.

The diagnosis in the cases recorded seemed absolutely certain. The characteristic high color index was present in each one, normoblasts and megaloblasts were present in the blood smears. Roentgen-ray and all other modes of investigations failed to point to any other diseased process. In 1 case the diagnosis was verified at autopsy.

All hematinic medications (iron, arsenic, bone-marrow, etc.) were discontinued one week prior to the administration of the germanium, and were not exhibited until three weeks after the last dose of the drug was given.

In all 3 cases the germanium was administered at the rate of 100 mg. per kilo of body weight.

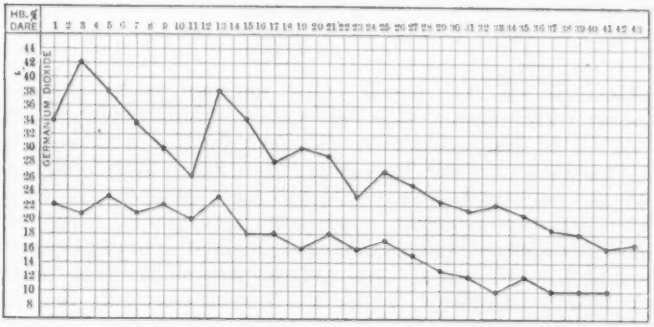


CHART I.—Hemoglobin and red blood cell count in Case I. (H. K.)

CASE I.—H. K., male, aged forty-one years; pernicious anemia of two years' duration. Patient was previously transfused several times with temporary amelioration of condition. At the time the administration of the germanium was started, the patient's hemoglobin was 22 per cent and the erythrocytes were 1,100,000. 100 mg. of germanium per kilo of body weight was administered and

a total of 5 gm. was administered in the course of three weeks. Approximately, 300 mg. was given hypodermically twice a week, while the rest of the substance was administered in solution by mouth. In spite of this treatment, the patient's condition continued to grow worse. The hemoglobin fell to 10 per cent (Dare) and the erythrocytes numbered 670,000.

TABLE I. DETAILS OF BLOOD EXAMINATION IN CASE I (H. K.)

Day No.	Hb.	R. B. C.	W.B.C.	Poly.	Lymph.	Mon.	Eos.	Bas.	Nucl. Reds.
1	22	1,100,000	5400	61	30	7	1	1	Many.
3	21	1,300,000	5600	60	28	10	2	0	"
5	23	1,200,000	5200	58	34	7	1	0	"
7	21	1,080,000	4800	64	32	3	0	1	"
9	22	1,000,000	5200	66	30	4	0	0	"
11	20	1,000,000	6000	60	28	9	2	1	"
13	23	1,200,000	6100	59	34	6	1	0	"
15	18	1,000,000	5400	54	32	12	1	1	"
17	18	950,000	5200	50	38	10	2	0	"
19	16	1,000,000	4800	58	36	5	0	1	"
21	18	960,000	5100	63	32	4	1	0	"
23	16	840,000	4600	62	30	7	1	0	"
25	17	920,000	4200	70	19	9	1	1	"
27	15	860,000	5200	64	26	8	1	1	"
29	13	820,000	4000	63	27	9	1	0	"
31	12	790,000	4800	59	30	1	0	1	Numerous.
33	10	800,000	4400	62	29	8	1	0	"
35	12	760,000	5400	58	31	9	1	0	"
37	10	720,000	6000	60	33	7	0	0	"
38	10	700,000	4100	64	31	4	1	0	"
41	10	650,000	4800	65	30	4	1	0	"

CASE II.—B. D., female, aged forty-six years; pernicious anemia. This patient was first seen in March, 1922. At the time of the first examination the hemoglobin was 16 per cent; erythrocytes, 1,200,000; leukocytes, 5200; with a differential count showing polymorphonuclears, 54 per cent; lymphocytes, 40 per cent; large mononuclears, 5 per cent; eosinophiles, 1 per cent; many normoblasts and megaloblasts, marked granular degeneration of the erythrocytes and polychromatophilia. The patient was put on germanium dioxide and treated essentially the same as in the first patient. There was no improvement following the administration of the compound (Table II). After administering the germanium for three weeks it was discontinued and three weeks later iron cacodylate, ½-grain ampoules, was commenced intramuscularly, administered twice weekly. Considerable improvement was observed at the end of two weeks and blood changes became apparent very promptly.

TABLE II. HEMOGLOBIN AND RED BLOOD CELLS IN CASE II (B. D.)

Day No.	Hemoglobin Per cent	Red Blood Cells	Day No.	Hemoglobin Per cent	Red Blood Cells
1	16	1,200,000	33	10	1,050,000
3	14	1,100,000	35	11	920,000
5	16	1,100,000	37	10	940,000
7	14	1,200,000	39	12	980,000
9	12	1,000,000	41	14	1,000,000
11	13	1,050,000	43	13	1,060,000
13	15	1,050,000	45	14	1,900,000
15	13	1,000,000	47	15	1,120,000
17	11	980,000	49	16	1,400,000
19	13	1,100,000	51	14	1,610,000
21	14	1,000,000	53	18	1,880,000
23	15	960,000	55	20	1,900,000
25	12	940,000	57	21	1,860,000
27	11	980,000	59	22	2,000,000
29	10	1,000,000	61	24	2,100,000
31	9	1,000,000	63	24	1,980,000

TABLE III. HEMOGLOBIN AND RED BLOOD CELLS IN CASE III (W. W.)

Day No.	Hemoglobin Per cent	Red Blood Cells	Day No.	Hemoglobin Per cent	Red Blood Cells
1	16	1,050,000	33	12	1,000,000
3	16	1,040,000	35	14	1,110,000
5	15	1,000,000	37	15	1,200,000
7	14	1,100,000	39	16	1,210,000
9	16	1,200,000	41	16	1,200,000
11	17	1,210,000	43	17	1,250,000
13	18	1,240,000	45	18	1,260,000
15	16	1,200,000	47	20	1,280,000
17	16	1,100,000	49	22	2,000,000
19	15	1,120,000	51	24	2,200,000
21	14	1,200,000	55	25	2,200,000
23	14	1,100,000	58	24	2,300,000
25	13	1,100,000	62	23	2,400,000
27	12	1,050,000	65	26	2,000,000
29	12	1,100,000	68	28	2,400,000
31	13	1,100,000			

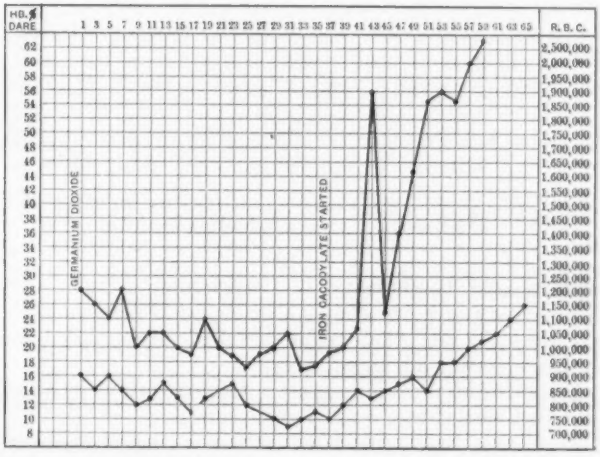


CHART II.—Hemoglobin and red blood cells in Case II (B. D.) showing effect of germanium and iron cacodylate respectively.

Case III.—W. W., male, aged thirty-eight years; pernicious anemia. From the history of the case, the patient has had two previous exacerbations. He had the usual hematinic remedies, but no hypodermic administrations of iron and arsenic; no transfusions. The patient had no medication whatever for three weeks prior to the time when he was first seen. At the first examination the hemoglobin was 16 per cent (Dare); erythrocytes, 1,050,000; leukocytes, 4800; with a differential count of polymorphonuclears, 61 per cent; lymphocytes, 31 per cent; large mononuclears, 6 per cent; eosinophiles and basophiles, each 1 per cent; a moderate number of normoblasts and megaloblasts; marked granular degeneration and polychromatophilia. The germanium was administered as in Case I, and 4.5 gm. were used in four weeks' time.

Three weeks after the last dose of germanium, iron cacodylate, $\frac{1}{2}$-grain ampoules, was administered hypodermically twice a week for three weeks. Table III shows the details of the blood findings in this case.

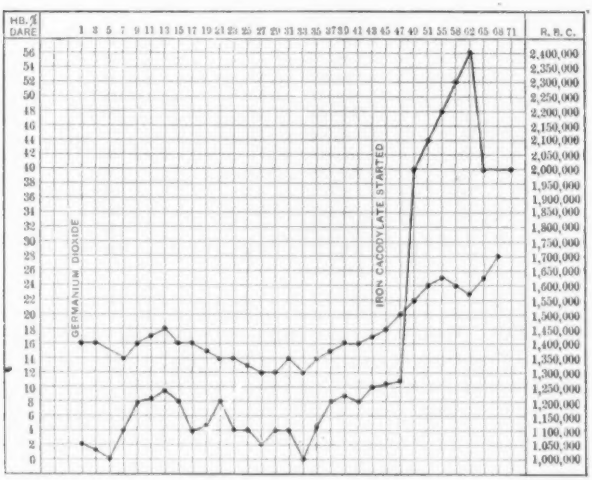


Chart III.—Hemoglobin and red blood cells in Case III (W. W.) showing effect of germanium and iron cacodylate respectively.

Summary and Conclusions. 1. Germanium dioxide, obtained from a reliable source, was employed in 3 cases of pernicious anemia. One of the cases was what might be called far advanced and the other 2 moderately advanced cases.

2. Diagnosis of pernicious anemia seemed certain in all of the cases. In 1 case it was verified at necropsy.

3. No clinical improvement was noticed in any of the cases and

the hemoglobin and erythrocytes showed no increase during the period of observation.

4. Arsenic and iron, administered hypodermically after the germanium was stopped, lead to an increase of hemoglobin and erythrocytes, also to symptomatic amelioration.

5. In pernicious anemia, germanium dioxide when administered by mouth and hypodermic injection led to no beneficial results. Arsenic and iron seemed definitely superior to germanium in this disease.

THE ANTISEPTIC AND BACTERICIDAL PROPERTIES OF ISOPROPYL ALCOHOL.

By Dudley H. Grant, M.S.

ELIZABETH, N. J.

Isopropyl alcohol (also known as secondary propyl alcohol, dimethyl carbinol and petrohol) has been placed on the market in commercial quantities only during the last two or three years. In the United States, it is a by-product of the petroleum and natural gas industries, while in Germany it is produced by the reduction of acetone, which is made by a series of reactions from calcium carbide.

Isopropyl alcohol boils at 82.26° C., and has a density of 0.7808 at $\frac{25°}{4°}$. Like ethyl alcohol, it forms a constant-boiling mixture with water. This mixture contains 91.1 per cent by volume of isopropyl alcohol, boils at 80.4° C., and has a density of 0.8158 at $\frac{20°}{4°}$. This is the form in which the alcohol is usually marketed.

Isopropyl alcohol is similar in many of its properties to ethyl alcohol, though it appears, according to what few data have been published,[1] to produce no exhilarating effect when ingested, and has, moreover, an unpleasant taste, except in high dilution. No motive could, therefore, exist for attempting to employ it as a beverage.

The entry of isopropyl alcohol into commerce and its suggested use as a substitute for ethyl alcohol in cosmetics and external medicine has raised the question of its physiological properties.

The toxicity of isopropyl alcohol toward higher animals has been investigated by Macht,[2] Burton-Opitz,[1] Boruttau[3] and a number of earlier observers. Their results, obtained by various methods on a number of different animals, indicate that isopropyl alcohol is somewhat more toxic than ethyl alcohol, but not more than twice as toxic as ethyl alcohol. Its toxicity is slightly less than that of the isomeric normal propyl alcohol, and much less than that of the butyl and amyl alcohols. This is in accordance

with the well-known law of Richardson, which states that the toxicity of alcohols increases with their molecular weights.

Ingested isopropyl alcohol does not produce an acute secondary intoxication, due to its metabolic products, as does methyl alcohol. It has been shown, furthermore, to have no noticeable harmful effect upon the human skin.[1 3]

The comparative bactericidal power of isopropyl alcohol might be expected to run roughly parallel to its toxicity. That this is the case is confirmed by the three published investigations bearing on this subject which a search of the literature has revealed.

Wirgin[4] performed a long series of comparative experiments upon the power of various alcohols, in various concentrations, to inhibit the growth of, and to kill, cultures of Micrococcus pyogenes aureus.

Growth in bouillon cultures at 37° C. was inhibited by 8 per cent of methyl alcohol, 6 per cent of ethyl, 4 per cent of propyl (either normal or iso-), 2 per cent of butyl (either normal or iso-) or 1 per cent of normal amyl alcohol.

Suspensions of Micrococcus pyogenes aureus were dried on quartz pebbles and subjected to the action of various alcohols in different concentrations for various lengths of time, then rinsed, shaken with sterile water and plated out on agar. Isopropyl alcohol, at a concentration eight times normal (*i. e.*, 48 per cent), effected complete sterilization in five minutes, while ethyl alcohol of the same molecular concentration did so in ten minutes, and methyl alcohol failed to sterilize during fifteen minutes, as did 1 per cent phenol. A normal (*i. e.*, 6 per cent) solution of isopropyl alcohol failed to kill off the dried cocci in fifteen minutes. Propyl alcohol, either normal or iso-, in 20 per cent concentration, killed the cocci in a few minutes, while 20 per cent ethyl alcohol hardly did so in twenty-four hours.

Wirgin also investigated the optimum concentration of methyl, ethyl and normal propyl alcohols for effectiveness against Micrococcus pyogenes aureus dried on silk threads and in moist suspension. One minute's immersion secured sterilization of the silk threads in the case of 60 per cent ethyl and methyl alcohols, and in propyl alcohol of all concentrations from 20 to 60 per cent, inclusive. Highly concentrated alcohols (*i. e.*, stronger than 70 or 80 per cent) were found, as is well known, to be ineffective against dried bacteria. The minimum sterilizing concentration, for one minute's action, against moist cocci, was 60 per cent for methyl alcohol, 50 per cent for ethyl and 20 per cent for propyl. In this case, the higher concentrations were also effective. Unfortunately, isopropyl alcohol was not used in this test, but the close similarity between the bactericidal properties of the two propyl alcohols observed by Wirgin in all the other tests makes it probable that its effective concentration would be about the same.

Wirgin found the bactericidal action of the alcohols to be especially notable when Micrococcus pyogenes aureus dried in blood serum was employed. The penetrating property of alcohols, together with the fact that they do not coagulate serum proteins, made their solutions (at optimum concentration) distinctly more effective than 0.2 per cent mercury bichloride or 5 per cent formalin, and approximately equal to 3 per cent phenol, 2.5 per cent cresol plus soap, or 0.1 per cent iodine trichloride solutions.

Considering aqueous alcohols as a class, Wirgin ranks 30 per cent propyl or isopropyl first, 60 per cent ethyl next, 60 per cent methyl next, and saturated solutions of the higher alcohols next, in bactericidal efficiency. The butyl and amyl alcohols, while more effective in equal concentration than the lower alcohols, are not, like them, miscible with water in all proportions, and are consequently limited in application.

From the standpoint of practical application, the propyl alcohols (isopropyl and normal propyl) occupy an especially favorable position in that they are the alcohols of the highest molecular weight that are still miscible with water in all proportions.

Bernhardt, Director of the Bacteriological Laboratory of the Friedrichshain Hospital, Berlin, has recently published[5] an investigation of isopropyl alcohol as a means for disinfecting the hands in surgical and gynecological practice. Staphylococcus pyogenes aureus, Bacillus coli communis, Bacillus anthracis and Bacillus subtilis were used as test organisms. Inhibition of bacterial growth was effected at between 3 and 6 per cent concentration of isopropyl alcohol. Dilute isopropyl alcohol killed dried anthrax bacilli and staphylococci in two to five minutes. A 40-per-cent concentration of isopropyl alcohol was found to be approximately equivalent to 60 per cent ethyl alcohol.

Bernhardt then carried out a series of practical tests by soiling the hands of several subjects with Bacillus coli cultures, allowing them to dry and then, without washing, rubbing them with isopropyl alcohol (20 cc on gauze; later, 10 cc was found sufficient). One finger, as a control, untreated with alcohol, but dipped into nutrient agar, demonstrated extreme contamination, over 20,000 bacteria per finger.

The alcohol, in 80 per cent and 60 per cent concentration, was rubbed upon the hands until it evaporated. In a series of 20 experiments, this resulted in complete sterilization in 60 per cent of the cases, extensive reduction (less than 10 surviving bacilli) in 20 per cent, and considerable reduction (10 to 1000 surviving bacilli) in 20 per cent. This approximates the action of ethyl alcohol. Isopropyl alcohol is effective, however, in lower concentrations than is ethyl. Bernhardt emphasizes, as have previous authors, the wide variation in individual hands, with respect to ease of disinfection. He recommends that isopropyl alcohol of 50

per cent be used upon dry hands, and of 70 to 80 per cent upon moist hands, and concludes that it is a complete substitute for ethyl alcohol, for this purpose. He did not, apparently, investigate the effectiveness of isopropyl alcohol at its optimum concentration, *i. e.*, 30 to 50 per cent.

Seifert[6] tested the fermentability of various alcohols by Bacterium pasteurianum and Bacterium kuetzingianum, two acetifying organisms isolated by Hansen from Mycoderma aceti. Isopropyl alcohol showed a marked inhibiting effect upon these bacteria, no growth being observed during eight weeks in the presence of 1 per cent of the alcohol. Yeast decoction and unhopped beer wort were used as media. The same organisms fermented 5 per cent ethyl, 3 per cent normal propyl and 1 per cent normal butyl and isobutyl alcohols, and grew in a medium containing 2 per cent methyl alcohol, though without oxidizing the alcohol. Toward the vinegar-forming bacteria, therefore, isopropyl alcohol appears to have the greatest antiseptic power of all the lower alcohols.

Of interest in this connection is the work of Pringsheim,[7] who demonstrated that isopropyl alcohol is formed by an organism, Clostridium americanum, isolated by him from potatoes, and producing also normal butyl alcohol and butyric acid when grown on potato mash. This datum confirms the scattered and questioned references[8] to the presence of isopropyl alcohol in fusel oil, which is shown to be due to an abnormal fermentation involving butyric acid bacilli.

While not dealing with isopropyl alcohol, the work of Saul[9] has an inferential bearing. This investigator subjected sporulated cultures of Bacillus anthracis, as well as other organisms, to the action of boiling alcohols of different concentrations. He employed only methyl, ethyl and normal propyl alcohols, and found all three to be useless when anhydrous, but effective in lower concentrations, when the duration of boiling was sufficient. The aim of Saul's work was to find an easy and effective method for sterilizing surgical sponges, and he concluded that boiling 30 per cent propyl alcohol was the best agent tried. It is a plausible assumption that isopropyl alcohol might serve as well.

Since isopropyl alcohol has come into commerce in this country, samples of it have been distributed to several physicians and hospitals, for use as a massage medium and surgical antiseptic, with general satisfaction. It has also found employment as a preservative for museum specimens and for surgical catgut.

Summary and Conclusions. 1. Isopropyl alcohol is a nonpotable alcohol, somewhat more toxic than ethyl alcohol, but not more than twice as toxic as ethyl alcohol.

2. Isopropyl alcohol is a more powerful bactericide and antiseptic than ethyl alcohol toward the organisms so far studied (Staphylococcus pyogenes aureus, Bacillus coli communis, Bacillus

anthracis, Bacillus subtilis and acetic acid bacteria). It is most effective in concentrations of 30 to 50 per cent.

3. Since it is not liable to be diverted for beverage use, and is not subject to burdensome taxes and restrictions, isopropyl alcohol may advantageously replace ethyl alcohol, under some circumstances, as a surgical antiseptic and preservative.

BIBLIOGRAPHY.

1. Grant, D. H.: The Pharmacology of Isopropyl Alcohol Jour. Lab. and Clin. Med., 1923, **8**, 382.
2. Macht, D. I.: A Toxicological Study of Some Alcohols, with Especial Reference to Isomers, Jour. Pharmacol. and Exper. Therap., 1920, **16**, 1.
3. Boruttau, H.: Die Verwendung von Isopropylalkohol zu hygienischen und kosmetischen Zwecken, Deutsch. med. Wchnschr., 1921, **47**, 747.
4. Wirgin, G.: Vergleichende Untersuchung ueber die keimtoedtenden und die entwickelungshemmenden Wirkungen von Alkoholen, etc., Ztschr. f. Hygiene u. Infek., 1904, **46**, 149.
5. Bernhardt, G.: Ueber Isopropylalkohol als Mittel zur Haendedisinfektion, Deutsch. med. Wchnschr., 1922, **48**, 68.
6. Seifert, W.: Beitraege zur Physiologie und Morphologie der Essigsaeurebakterien, Centralbl. f. Bakteriol., 1897, **3**, 337.
7. Pringsheim, H.: Ueber den Ursprung des Fuseloels, etc., Centralbl. f. Bakteriol., 1905, **15**, 300; Ueber die Unterdrückung der Fuseloelbildung, etc., Biochem. Ztschr., 1908, **10**, 490; 1908, **16**, 243.
8. Rabuteau: De la présence des alcools isopropylique . . . dans les huiles et les alcools des pommes de terre, Compt. rend. Soc. de biol., 1878, **5**, 357. Schupphaus, R.: On the Alcohols of Fusel Oil, Jour. Am. Chem. Soc., 1892, **14**, 45.
9. Saul, E.: Ueber die Desinfektionsenergie siedender Alkohole, Arch. f. klin. Chir., 1898, **56**, 686.

STUDIES ON THE REACTIONS OF ASTHMATICS AND ON PASSIVE TRANSFERENCE OF HYPERSUSCEPTIBILITY.

By Arent de Besche, M.D.,
CHRISTIANIA, NORWAY.

1. Cutaneous and Other Reactions in Bronchial Asthma. According to investigations by Walker,[1] Rackemann, Freeman, de Besche and others, certain forms of asthma are regarded as expressions of hypersusceptibility to foreign proteins that may gain entrance into the body. Such forms of asthma might be called anaphylactic asthma. In this article, certain results are reported of investigations on asthmatics by means of protein extracts of timothy pollen, of substances from various animals (horse, dog, cat, chicken, sheep, crabs, lobster, honey, milk, egg, fish, potato, oats, rye, rice, staphylococci, streptococci, Micrococcus tetragenus, strawberries, nuts, apples, pears). Altogether, cutaneous reactions of 86 asthmatics have been studied. Careful clinical examination with roentgen photographs and special examination of the nose and throat were made in each case of suspected asthma, and all cases of dyspnea that might be associated with

cardiorenal diseases and organic lung changes have been eliminated. Paroxysmal dyspnea with sibilant rales in the chest without any demonstrable anatomical cause has been the standard

TABLE I.—CUTANEOUS AND OTHER REACTIONS IN THIRTY-FIVE ASTHMATICS.

Patients.				Horse.			Cat.			Dog.													
No.	Age.	Sex.	Timothy pollen.	Serum.	Walker's extract.*	Eye (de Besche).	Serum.	Walker's extract.*	Eye (de Besche).	Serum.	Walker's extract.*	Eye (de Besche).	Egg.	Fish.	Wheat.	Staphylococci.	Streptococci.	M. tetragenus.	Strawberries.	Nuts.	Apples, pears	Crab.	Honey.
1	45	M	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
2	24	F	○	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
3	25	F	○	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
4	42	M	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
5	22	M	○	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
6	49	M	○	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
7	29	F	○	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
8	30	M	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
9	37	F	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
10	10	M	+	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
11	14	M	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
12	45	M	+	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
13	16	F	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
14	7	F	+	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
15	22	M	+	○	○	+	○	○	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○
16	35	M	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
17	27	M	○	○	○	○	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○
18	38	M	○	○	○	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○
19	22	F	+	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○
20	29	M	+	+	+	+	+	+	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○
21	43	F	+	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	+
22	24	F	+	○	○	+	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○
23	22	F	+	+	+	+	○	○	○	○	○	○	○	+	○	○	○	○	+	○	○	○	○
24	9	M	+	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	○
25	7	M	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○	○	○	+	○	○
26	11	M	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	+	○
27	52	M	+	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○
28	30	F	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○
29	26	F	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○
30	40	F	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	+	+	○	○
31	70	M	+	○	+	+	○	○	○	○	○	○	○	○	○	+	○	○	○	○	+	○	○
32	52	M	○	○	○	○	○	○	○	○	○	○	○	○	○	+	+	○	○	○	○	○	○
33	45	M	○	○	○	○	○	○	○	○	○	○	○	○	○	+	+	○	○	○	○	○	○
34	52	M	○	○	○	○	○	○	○	○	○	○	○	○	○	+	+	○	○	○	○	○	○
35	51	F	○	○	○	○	○	○	○	○	○	○	○	○	○	+	+	+	○	○	○	○	○

In addition, all 35 patients were negative to chicken, sheep, milk, potato, oats, rye, rice, lobster, crawfish.

* Prepared by Arlington Chemical Company.

for the diagnosis in each case. As shown in Table I, which gives the positive results, the most frequent reaction was obtained with extracts of horse proteins, 23 in all, and in some of these cases,

reactions were obtained also with other substances. It is interesting that the results corresponded either with the experiences of the patients themselves as to the causes of their asthma or with results of experiments that I made upon the basis of the reaction. It appears that several substances may cause asthma in the same patient: Patient 23 becomes asthmatic from emanations of flowers and from contact with horses as well as on eating fish or strawberries, and Patient 25, a seven-year-old boy, is made asthmatic on eating eggs and apples. A sister of this patient, upon eating these things, develops urticaria but not asthma. Patient 15 develops asthma and coryza on contact with horses and dogs; Patient 18, on contact with horses and cats; and Patient 20 on contact with horses, dogs and cats. The patients reacting to bacterial extracts were old asthmatics with chronic bronchitis. Three patients reacted to extracts of nuts; one of them developed typical asthma upon eating nuts, with swelling of the oropharyngeal mucous membrane and of the conjunctiva and running of the nose; the others developed less-marked pulmonary symptoms but marked oronasopharyngeal and conjunctival symptoms upon eating nuts; one developed similar symptoms also from eating apples and pears.

Reactions were made according to certain methods of my own also. The patients who were susceptible to extracts of horse materials were tested for skin reactions to horse serum and for conjunctival reactions upon touching the conjunctiva with a finger that had been passed over the hair of a horse or other animal, the finger thus carrying a little dandruff or sweat. This conjunctival reaction is referred to hereafter as the eye reaction (de Besche). Of the 23 asthmatics giving reactions to horse extracts, 10 gave cutaneous reactions to horse serum, 17 reacted to Walker's extracts, and all gave the eye reaction. These tests were made at the same time in each case. Of the patients sensitive to cat material, 3 gave positive reactions to all tests, 1 only the eye reaction; the details of the reactions to dog extract may be seen in the Table. On the whole, in cases of asthma depending apparently upon contact with horses, cats and dogs, the eye reaction gives the largest number of positive results, next the test according to Walker's method, while less than half reacted to horse serum on cutaneous injections. Comparing the degrees of hypersusceptibility of the patients giving the eye reaction and skin reaction with horse serum, those reacting to the latter must be regarded as the more sensitive. It has been said that asthmatics that give cutaneous reaction to horse serum should not be injected with horse serum, because of the danger of violent symptoms, whereas asthmatics that give reactions with Walker's extracts only may be injected without danger. All my cases of horse asthma have been tested for cutaneous reactions to sheep serum,

but with uniformly negative results, suggesting that antidiphtheria serum developed in sheep would be free from danger. Certain patients hypersusceptible to other substances were tested further as to eye and skin reactions with the material itself or with juice pressed out of it, and in only 2 cases, giving positive reactions, was there failure to react to Walker's extracts.

Most of the patients in whom positive reactions developed knew beforehand the conditions under which asthmatic symptoms usually would arise, but this was not true of all. Thus, Patient 4 and Patient 20 did not realize until they were eighteen and twenty-seven years old, respectively, that their asthma depended upon contact with certain animals. Others (Patients 2, 11, 15 and 26) knew nothing of the influence the materials to which they reacted played in the production of the asthma from which they suffered, and they derived great benefit from the knowledge thus obtained. It should be noted that, as my material is selected material, it should not be made the basis for any statistics of the different kinds of asthma. Some patients seem to have known since early childhood that they were susceptible to contact with horses or to certain foods, while to others this did not become apparent until much later. Patient 4, a woman, aged twenty-four years, who lived in the country and came in close contact frequently with horses, did not begin to suffer from asthma until seventeen years of age, and shortly afterward she realized that the asthma was connected in some way with horses. Three patients are farmers, who began to suffer from asthma, due to contact with horses, after reaching adult age. Patient 30, a woman, aged forty years, could eat apples, pears and nuts without harm until thirty-six years of age, when she began to suffer from paroxysms of asthmatic symptoms with increased nasal secretions and swelling of the eyes, and in the course of the next two or three years it became apparent to her that these symptoms arose only after the consumption of the articles mentioned. In many cases of hay fever and asthma, a familial disposition to hypersusceptibility is present because the majority of the patients state that several members of their families suffer from these diseases. The similarity of these asthmatic conditions, particularly horse asthma, to experimental anaphylaxis is shown by the fact that one patient, who suffered from anaphylactic shock after injection of antidiphtheria (horse) serum, remained free from the usual asthmatic symptoms when in contact with horses for about three months; in other words, a condition of antianaphylaxis was produced by the injection of the horse serum. Bacon and Wright[2] made similar observations, and Walker and others have shown that small quantities of horse proteins may produce a temporary insusceptibility in horse asthmatics. The remarkable case of asthma, following injection of horse serum, described by Walker, seems so far to remain quite unique. As

stated in greater detail in the following, I have succeeded in making guinea-pigs susceptible to horse serum and also to cat serum, by injecting them with the serum of patients with horse and cat asthma. These results are quite analogous to the noteworthy case, described by Ramirez,[3] of the patient who was transfused with blood and subsequently developed asthma dependent upon contact with horses. It was found then that the donor suffered from a pronounced form of horse asthma.

2. Passive Transference of Hypersusceptibility by the Serum of Certain Asthmatic Persons. When the blood of an animal, made hypersensitive by the injection of a foreign protein, is injected into a normal animal, the normal animal may become hypersensitive to the same protein. This is passive anaphylaxis. As a rule, some hours must elapse after the injection before passive anaphylaxis becomes demonstrable; in the case of guinea-pigs, from six to twenty-four hours may elapse; in dogs, Richet found that passive anaphylaxis could be demonstrated after two hours. It is believed that this latent period corresponds to the time required for the antisubstances in the injected serum to become anchored to the cells of the tissues. It has been found possible to transfer anaphylactic conditions in man to guinea-pigs. Thus, Grysez and Bernard,[4] as well as Achard and Flandin,[5] found that the blood of patients, injected with therapeutic serum and who, on that account, had become hypersensitive to the serum, when injected into guinea-pigs, made them anaphylactic with respect to the same serum. Longcope and Rackemann[6] obtained similar results with the serum of patients who had been injected with large quantities (180 to 360 cc) of antipneumococcus serum (horse serum); in a large number of cases, the guinea-pigs so injected became anaphylactic with respect to horse serum. In a case of urticaria in man from eating pork, Bruch,[7] by injecting the patient's serum into guinea-pigs, rendered them hypersensitive to swine serum. Schultz and Larson[8] report cases of hypersusceptibility to milk in children and the production of passive anaphylaxis in guinea-pigs by the injection of the serum of such children. The question arises whether the serum of an asthmatic patient, who is hypersensitive with respect to a particular protein, can render guinea-pigs anaphylactic to the same protein. As only scattered observations appear to have been made in regard to this question, it seemed to me advisable to publish the results of further observations.[9] In most of my cases, it concerns persons who were hypersensitive to emanations from horses; in 1 case, the patient was hypersensitive to cats. From 1 to 5 cc of the serum of the patient was injected intraperitoneally in guinea-pigs and after twenty-four to forty-eight hours, the guinea-pigs were then injected with horse or cat serum, usually in quantities of 0.5 cc intravenously or of 3 to 5 cc intraperitoneally. Furthermore, 0.1 cc of serum was injected

intracutaneously in the guinea-pigs with a view to studying the local reactions.

CASE I.—Woman, aged twenty-three years, suffered from horse asthma since her sixteenth year. By going into a stable for horses, driving with horses, etc., marked dyspnea would develop that might last for several days. When removed from horses and things that had been in contact with horses, she was free from symptoms. Other animals did not have any such effects. When the conjunctiva was touched with the finger that previously had stroked a horse, a strong reaction would develop; she also gave a marked cutaneous reaction with Walker's extract of horse dandruff and with horse serum. The patient's serum, 5 cc, was injected intraperitoneally into a guinea-pig, and twenty-four hours later the guinea-pig received 0.5 cc of horse serum intravenously; in five minutes, marked anaphylactic shock developed. Another guinea-pig received 2.5 cc of the patient's serum intravenously, and forty-eight hours later 0.5 cc of horse serum intravenously; this animal also developed definite symptoms of anaphylactic shock. Before being injected intravenously, both animals received 0.1 cc of horse serum intracutaneously, and in 1 of them a large wheal, 1 cm. in diameter, developed, but the other gave no definite reaction.

CASE II.—Man, aged thirty-three years, asthmatic from earliest childhood when in contact with horses; suffered also from hay fever and asthmatic attacks on eating strawberries. A strong conjunctival reaction developed from the touch of a finger that had been passed over the hair of a horse. He gave a marked cutaneous reaction with Walker's extract of horse dandruff and with horse serum as well as with extracts of pollen and strawberries. The patient's serum, 5 cc, was injected into a guinea-pig intraperitoneally; twenty-four hours later 3 cc of horse serum were injected intraperitoneally and was followed by marked anaphylactic shock in fifteen minutes. A similar result followed the injection of 0.5 cc of horse serum intravenously in another guinea-pig which had received 3 cc of the patient's serum intraperitoneally forty-eight hours before. In 1 of the animals, 0.1 cc of horse serum produced, on intracutaneous injection, a large wheal.

CASE III.—Man, aged thirty years, asthmatic from earliest childhood when near horses; strong conjunctival and cutaneous reactions developed when tested, as the previous two patients; guinea-pigs injected with the patient's serum intraperitoneally, 5 cc in each case, and reinjected in the same way with the same quantity of horse serum in twenty-four hours, developed marked anaphylactic shock, and in one of the animals a large wheal developed on intracutaneous injection of 0.1 cc of horse serum.

CASE IV.—Man, aged thirty-eight years; since childhood swelling of the conjunctiva and cutaneous wheals developed whenever he came in contact with cats; similar symptoms, but less marked, also developed from contact with horses; asthmatic symptoms from time to time. Touching the conjunctiva with a finger after stroking a cat gave rise to redness, edema, and flow of tears; after a similar test after stroking a horse, redness and itching developed. When scratched by a cat, large wheals would develop. After the intraperitoneal injection of 5 cc of the patients serum and forty-eight hours later an injection of 3 cc of cat serum, marked symptoms of anaphylactic shock developed, while the intraperitoneal injection of 5 cc of cat serum in a fresh guinea-pig was without any special effect.

CASE V.—Man, aged forty-three years, horse asthma from childhood and also suffered from hay fever, sometimes with marked asthmatic symptoms. He gave strong conjunctival and cutaneous reactions to horse proteins. A guinea-pig injected intraperitoneally with 1 cc of the patient's serum, and twenty-four hours later with 0.5 cc of horse serum intravenously, developed marked anaphylactic shock; another guinea-pig injected intraperitoneally with 5 cc of the patient's serum, and forty-eight hours later with 5 cc of horse serum, developed only some dyspnea and a subnormal temperature. Both these animals developed large wheals in the skin on the intracutaneous injection of 0.1 cc of horse serum twenty hours after the injection of the patient's serum.

CASE VI.—A man, aged forty-two years, asthmatic since childhood, apparently dependent upon horse emanations; marked eye reaction and marked skin reaction to extract of horse dandruff, but no reaction upon intracutaneous injection of horse serum. Guinea-pigs injected intraperitoneally with 5 cc of the patient's serum gave no anaphylactic reaction upon intravenous or intraperitoneal injection of horse serum twenty-four hours later, and no cutaneous reaction to horse serum.

CASE VI *b*.—Woman, aged twenty-nine years, asthmatic at times as child and since eighteen years old has suffered from asthma when in contact with horses; she gave a strong eye reaction upon touching conjunctiva with a finger that had been passed over a horse; also cutaneous reaction with extract of horse dandruff, but not with horse serum; no anaphylactic symptoms and no cutaneous reaction in guinea-pigs injected with the patient's serum and reinjected with horse serum.

CASE VII.—Man, aged forty-four years, asthmatic since twenty years old when in contact with horses; strong eye reaction to finger

passed over the skin of a horse and strong skin reaction with extract of horse dandruff; no anaphylactic symptoms or cutaneous reaction upon injection of horse serum in guinea-pigs previously injected with the patient's serum.

CASE VIII.—Man, aged thirty-eight years, asthmatic since sixteen years old, depending upon horse emanations; his reactions were similar to those in Case VII, and the patient's serum did not render guinea-pigs anaphylactic to horse serum.

CASE IX.—Woman, aged twenty-three years, asthmatic since childhood from contact with horses; similar reactions as Cases VII and VIII; the patient's serum did not render guinea-pigs sensitive to horse serum.

In 4 cases, the serum of patients, suffering from asthma dependent on contact with horses, rendered guinea-pigs anaphylactic to horse serum. These patients gave eye and skin reactions to horse proteins. Analogous results were obtained in the case of 1 patient sensitive to cat emanations. In 5 other cases of horse asthma, the serum of the patient did not produce passive sensitization to horse serum in guinea-pigs. In these cases, the asthma appeared to be dependent upon horse emanations, but none of these cases gave any cutaneous reaction to horse serum, but all except one gave eye reactions by the de Besche method and skin reactions to horse dandruff. It appears that these patients were sensitive to substances in horse hair, dandruff and sweat and not to substances in horse serum.

I have emphasized that asthmatics,[10] in whom the disease appears to be dependent upon certain animal emanations, may give different local reactions, as observed also by others, some giving skin reactions with serum as well as with extract of hair and dandruff, while others do not react to the animal's serum. Whether this difference represents an essential difference in the nature of the conditions is difficult to say, but it would seem most reasonable to assume that it concerns differences in the degree of hypersensitiveness and that patients giving cutaneous reactions to serum are the more sensitive. This view is supported by my experiments in that in 4 instances of horse asthma and 1 of cat asthma, all these patients giving skin reactions to the corresponding serum, the patients' serum in each case produced passive anaphylaxis to horse serum in guinea-pigs.

As stated, Ramirez[2] describes an instance of a man who had not had asthma before, but who soon after transfusion began to have asthmatic attacks when in close contact with horses, and that it was found that the donor of the transfused blood suffered from horse asthma. In this case, the sensitive state was transferred

in the blood of one person to another. By means of the serum of asthmatics, I have succeeded in producing a local hypersusceptibility to horse serum in the skin of previously normal persons.

EXPERIMENT 1.—A man, aged forty-two years, was asthmatic since childhood upon coming in contact with horses; he gave a marked eye and skin reaction and reacted also to the cutaneous injection of horse serum. A perfectly healthy man, who did not suffer from asthma or urticaria, received 0.1 cc of the serum of the patient intracutaneously on the left forearm and also, for purposes of control, 0.1 cc of serum from a normal person and, in another place, 0.1 cc of salt solution. No reaction developed about any of these injections, and after twenty-four hours 0.1 cc of horse serum was injected intracutaneously in all the three places previously injected, and in the course of five minutes a large wheal, about 3 cm. in diameter, developed about the place in which the serum of the asthmatic patient had been injected. This wheal was surrounded by a hyperemic zone and itched greatly; it remained in full bloom for three or four hours and then disappeared fairly rapidly. The places injected with normal serum and salt solution showed no reaction from the injection of the horse serum.

EXPERIMENT 2.—Man, aged fifty-two years, has had hay fever since childhood, with asthma influenced by contact with horses; pronounced eye and skin reactions, as well as reaction to horse serum and to pollen; 0.1 cc of serum was injected intracutaneously in the arm of the patient's wife, also 0.1 cc from a normal person, and the same amount of salt solution; no reaction about any of the three points, and twenty-four hours later 0.1 cc of horse serum was injected intracutaneously, as in the previous case, with the result that an itching wheal, 4 cm. in diameter and surrounded by redness, developed about the point where the husband's serum had been injected; no reaction developed about the other points. In the other arm, also injected in three places in the same way, the injection of sheep serum twenty-four hours later did not produce any reaction. The subject of the experiment received 0.1 cc of the patient's serum intracutaneously in two other places and twenty-four hours later extract of pollen (Freeman's preparation) was injected in these places, and in one of them a large itchy wheal developed. The injection of pollen in other places of the skin gave no reaction.

EXPERIMENT 3.—Woman, aged thirty-six years, asthmatic since childhood, depending upon horses; sometimes, after contact with horses, urticaria would develop; marked eye reaction, as well as cutaneous reactions with extract of horse dandruff and horse serum; an experiment like that described in Experiment 1 was

made and with a similar result—the place where the patient's serum had been injected developed a large itching wheal upon the injection of horse serum twenty-four hours later.

EXPERIMENT 4.—Woman, aged twenty-eight years, asthmatic since childhood from contact with horses; marked eye and skin reactions; a sister of the patient, who did not have asthma, was injected intracutaneously with 0.1 cc of the patient's serum, in another place with the same quantity of normal serum, and in a third place with the same quantity of salt solution; twenty-four hours later 0.1 cc of horse serum was injected intracutaneously in all three places, but no reaction developed in any place.

EXPERIMENT 5.—Man, aged thirty-two years, asthmatic since ten years of age, apparently from sensitiveness to horses; he gave a marked eye reaction and skin reaction with extract of horse dandruff, but no reaction followed intracutaneous injection of horse serum; a brother, who was normal, was injected exactly in the same way as in Experiment 4, but no reaction developed.

In 3 of the experiments just described, the intracutaneous injection of serum from patients, suffering from asthma dependent upon substances from horses, produced a local hypersusceptibility to horse serum. This hypersusceptibility showed itself in the form of a wheal with hyperemia about the point where the horse serum was injected and where twenty-four hours before serum from the asthmatic patient had been injected. It seems quite clear that the asthmatic serum contained certain substances that produced a local hypersusceptibility.

These experiments and the experiments upon guinea-pigs show that certain asthmatics suffer from a condition that can be transferred passively. The patients with asthma, in which passive transfer of hypersusceptibility did not succeed, did not give any cutaneous reaction to horse serum, and may be regarded as less sensitive than those whose serum produced passive anaphylaxis.

Prausnitz and Kuster[11] report an instance of hypersusceptibility to fish protein, in which they produced a local hypersensitiveness in the skin of a normal person by the injection of the serum of the patient, but they did not succeed in similar experiments with the serum of hay-fever patients and of patients hypersusceptible to horse serum.

Conclusion. Taken in conjunction with the local skin and other reactions in asthmatics, the occasional severe symptoms of anaphylactic shock upon injection of asthmatics with horse serum and the demonstration in occasional cases of asthma of complement-binding bodies and precipitin in the serum, the results now presented, showing that the serum of asthmatics may be the means of trans-

ferring hypersusceptibility, strengthens materially the opinion that certain forms of asthma may be regarded as anaphylactic in nature.

REFERENCES.

1. Walker, I. C.: Bronchial Asthma, Oxford Med., 1920, **2**, 217.
2. Bacon and Wright: Jour. Am. Med. Assn., 1909, **52**, 1181.
3. Ramirez: Ibid., 1919, **73**, 984.
4. Grysez and Bernard: Compt. rend. Soc. de biol., 1912, **73**, 387.
5. Achard and Flandin: Ibid., 419.
6. Longcope and Rackemann: Jour. Exper. Med., 1918, **27**, 341.
7. Bruch: Berl. klin. Wchnschr., 1910, **47**, 517.
8. Schultz and Larson: Arch. Pediat., 1918, **35**, 705.
9. de Besche: Norsk Mag. f. Lägevidensk., 1918, **79**, 377; 1919, **80**, 830.
10. de Besche: Ibid., 1922, **83**, 361.
11. Prausnitz and Kuster: Centralbl. f. Bakteriol., 1921, **86**, 160.

DIFFERENTIAL DIAGNOSIS OF DIABETES.

By Henry J. John, M.D.,

CLEVELAND CLINIC, CLEVELAND, OHIO.

Often a patient with no subjective complaint is referred to a specialist because his family doctor or the examiner of a life insurance company has found sugar in the urine, either once only or repeatedly. The patient appears to be in perfect health, offers no complaint, no symptoms are apparent and there are no pathological physical findings. An examination of the urine discloses no sugar and examination of the fasting blood sugar shows a normal content.

What can one do in such a case? What can be said to the patient to allay his fears of diabetes and at the same time guard him against a possible later development of diabetes, the signs of which are absent at the moment? Can one say simply "I find no diabetes; you're all right" and let the patient go, only to return in a year or two with fully developed diabetes? Or shall he be condemned as a diabetic, in spite of the present negative findings, judgment being based merely on the sugar found in the urine by the referring doctor or the insurance examiner? In the latter case after following a restricted diet for a year or two, the patient may consult another specialist who may settle his problem by saying: "You are not diabetic; eat anything you wish."

Perhaps in no other disease is the establishment of a positive diagnosis in the early and in the borderline cases so difficult or a mistaken diagnosis so fraught with danger as is the case with diabetes and a final diagnosis in these cases often requires more than the common measures which are accessible to a man in general practice. It is therefore of importance that the general practitioner and the medical examiner understand what measures are essential

for the final establishment of a diagnosis in doubtful cases, and why dependence cannot be placed on urine examination alone, or even on the evidence of a single fasting blood-sugar estimation.

The point to be established is the ability of the individual to utilize (metabolize and store) carbohydrates. The presence of sugar in the urine tells only that the kidneys are permeable to sugar and by itself alone does not even disclose at what blood-sugar concentration this "overflow" takes place; for the permeability of the kidneys to glucose varies with the individual, and in different individuals, therefore, sugar may be found in the urine at any blood sugar concentration between 53 and 256 mg. per 100 cc.

It follows therefore that a progressive study of the blood sugar content—the establishment of the glucose tolerance curve—is the only method by which the ability of the individual to utilize carbohydrates can be established with certainty. That is, upon the glucose tolerance curve depends the establishment of the diagnosis of diabetes; moreover, the glucose tolerance curve discloses also whether or not the individual may be liable to develop diabetes and thus becomes a valuable prophylactic guide.

To illustrate the application of this procedure the following cases are cited:

CASE I.—A little boy, aged seven years, was brought in from a neighboring state where a diagnosis of diabetes had been made by his family physician, this diagnosis being based on the presence of sugar in the urine after a period of general malaise of several weeks duration.

Routine examination at this time showed no sugar in the urine, and a fasting blood sugar of 84 mg. per 100 cc—a low normal. The boy's mother stated, however, that for the preceding few days the boy had had a restricted diet. Were we justified on the basis of this examination in stating that this was not a case of diabetes since there was no sugar in the urine and no increased blood-sugar content?

In spite of the fact that the urine and fasting blood examination showed nothing abnormal, we proceeded to find how the boy could handle a heavy carbohydrate meal, 75 gm. of glucose (to an adult 100 gm. are given) in lemonade.

The glucose tolerance curve (Curve 1) shows a very gradual rise, its highest point being reached at the end of three hours, and just the beginning of descent at the end of four hours, so that were we to project this curve we would find that it would take from seven to nine hours for it to return to the starting point. In this case, therefore, a typical diabetic curve was secured. The glycosuria did not appear until the blood-sugar content had reached 272 mg. per 100 cc, showing that the point of kidney permeability to sugar lay somewhere between 84 and 272 mg. per 100 cc.

Thus, while we were not able to make any definite diagnosis in this case before the tolerance test was made, following that test we were able to say with confidence that it was a diabetic case, basing this conclusion on the proved lack of carbohydrate utilization. If even more definite evidence is desired, it can be secured by letting such a case go on for a few months on an unrestricted diet, when the typical picture of severe diabetes will develop and special diagnostic measures will not then be needed to confirm the diagnosis.

This boy was put on a gradually increasing diet, checked by repeated blood-sugar examinations so that today, after a two weeks' stay in the hospital, I am discharging him on a diet of 45 gm. of carbohydrate, 55 gm. of protein, and a total of 1700 calories on which his blood sugar remains normal, his last examination showing 73 mg. per 100 cc; no acetone.

This case illustrates not only the procedure whereby the diagnosis of diabetes is established, but also the importance of immediately and relentlessly pursuing the treatment, for especially in children, there is no time to lose. To my mind, diabetes and diphtheria in children have one point in common—they must be treated with promptness if we would get results. There is a critical period in diphtheria beyond which serum is of no avail; there is a critical period in diabetes in children beyond which treatment is of little or no avail. We know only too well the story of cases of advanced diabetes in children.

Case II.—A young foreign girl, aged twenty-six years, a housemaid, came in after following a diabetic regimen for three weeks. She had begun to feel that this was too difficult and wanted a confirmation of the diagnosis.

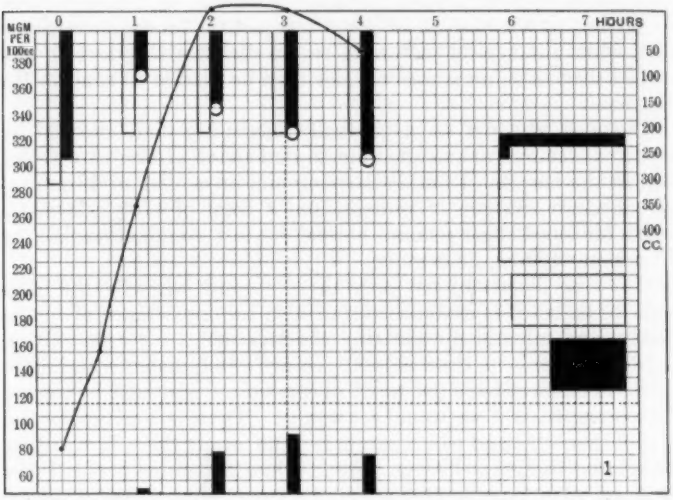
Her family history was of no significance. She had had measles in childhood, influenza four years ago. Her physical examination showed nothing abnormal; blood-pressure, 120–80. There was no sugar in the urine. The fasting blood sugar was 111 mg. per 100 cc; urea, 42 mg.; Wassermann, negative.

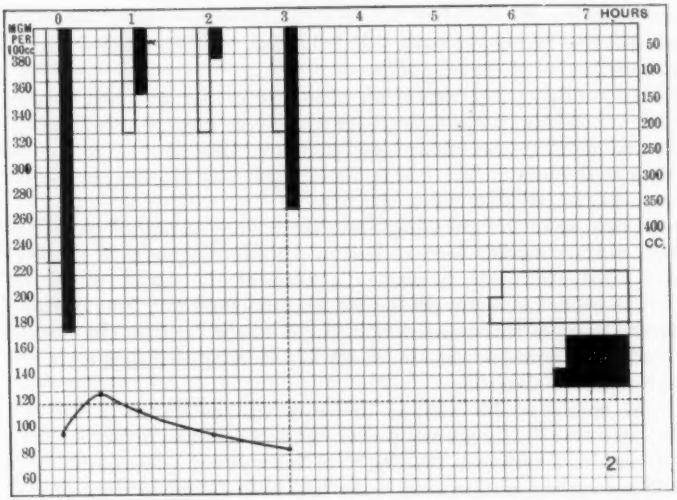
In this, as in the preceding case, there were no pathological findings, nothing upon which to base a definite diagnosis of diabetes and substantiate the primary diagnosis of the family physician. On the other hand the previous diagnosis could not be disproved on the basis of this examination, for it might be that the normal blood-sugar content was the result of the restricted diet as in the case reported above.

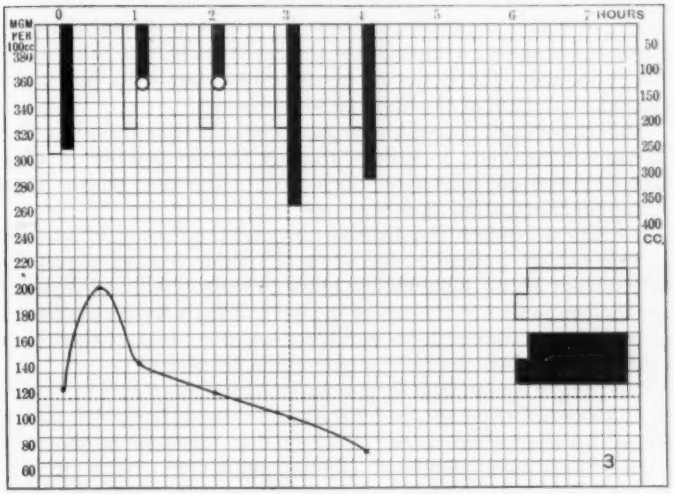
The results of the glucose tolerance test as shown in Curve 2 disclosed a perfectly normal carbohydrate tolerance, in fact a strong carbohydrate tolerance, proving that this was not a case of diabetes.

One cannot question that sugar had been found in the urine; it might have been a postprandial event. But to base the diagnosis

of diabetes on one urinary examination, and to stop there means subjecting the patient to a hard antidiabetic regimen which is not justifiable unless the diagnosis is confirmed.







The checkered columns at the top of the charts indicate the water intake; the solid black columns at the top indicate the urine output. The total intake and output during the period of four hours or more is indicated by a like marking at the lower right corner of the chart. The circles at the lower ends of the black columns indicate the presence of sugar in the urine.

The broken horizontal line opposite "120" is the normal level of blood sugar, *i. e.*, 120 mg. per 100 cc. The broken vertical line opposite "three hours" indicates the period within which, in normal individuals, the blood-sugar content again becomes normal after the ingestion of the standard dose of glucose. The heavy curve represents the blood-sugar content at the designated periods. The dots which break the glucose tolerance curve indicate the intervals at which blood was taken for sugar estimation. Each solid black column at the bottom of the charts represents the sugar content of the urine output indicated by the corresponding solid black column at the top of the chart. Each square included in these lower columns represents 1 gm. of sugar, and the total sugar output, the sum of these squares, is indicated by the solid black portion of the large square at the right of the chart, which includes 100 squares, representing 100 gm. of glucose, the total sugar intake.

Case III.—A plumber, aged thirty-four years, Jewish, married, came in for a consultation regarding a diagnosis of diabetes which had been made nearly two years before when sugar was found in his urine in an examination for life insurance. He was then referred to an internist who made a blood-sugar examination, with a normal finding, and then made a glucose tolerance test, which showed fasting blood sugar 110 mg. per 100 cc; one-half hour after the glucose ingestion, 193 mg.; one hour after, 200 mg.; two hours after, 158 mg., when the test was discontinued. There was no sugar in the urine at the beginning; 1.3 per cent at the end of one hour; 3.4 per cent at the end of two hours. On this finding, the diagnosis of diabetes was again made and the man was kept on a diabetic regimen for two years.

I made a glucose tolerance estimation at the end of this time, the results of which are shown in Curve 3. This is a normal tolerance curve and is almost a duplicate of the curve made from the findings two years ago. There was no glycosuria to start with, but it was present at the end of the first and second hours.

This curve made it possible for me to tell the man definitely that he was not a diabetic, in spite of the fact that he had been so diagnosed by two physicians and belonged to the race which has a strong predilection for diabetes.

In order to confirm the diagnosis beyond the shadow of a doubt, I subjected the patient to forced carbohydrate feeding, explaining to him that I was doing this in order to overtax his carbohydrate metabolism so that at the end of the week, if there were a deficiency, it would be manifested by a high blood-sugar content; if there were no deficiency, then the blood sugar would be normal.

The patient agreed, and for a week he feasted on pastry and cakes and all the carbohydrate food he could think of, for which he had longed for nearly two years. At the end of this time he showed a fasting blood-sugar content of 102 mg. per 100 cc. This certainly was sufficient evidence for considering the case to be a non-diabetic. For over a year his diet has been unrestricted and his blood sugar has been normal at each examination. The last examination showed a blood sugar content of 111 mg. per 100 cc.

Conclusion. The various case histories cited above emphasize the following important point in the diagnosis of diabetes:

If one bases his diagnosis on urinary examination alone there may result on the one hand danger to the patient if diabetes is present, and on the other, disadvantage and misery from a deficient diet, if the patient is not a diabetic; in the case of a mistaken insurance examination, not only the patient but his family also may suffer an injustice.

REVIEWS.

EPISCOPAL HOSPITAL REPORTS. Volume V. Pp. 506. Philadelphia: William J. Dornan.

THIS is a volume of splendid appearance and is well edited. About twenty-two members of a staff of fifty-seven act as contributors, together with about ten resident physicians. Most of the reports come from the surgical side of the institution with the name of the editor, Ashhurst, attached to twenty papers, about one-third of the volume. There is a lamentable lack of material from the medical staff. Most of the papers have appeared in some medical publications and are for the most part case reports. It is to be regretted that so active an institution as the Episcopal Hospital has had so little to offer. Perhaps the period of the war may be an excuse. The institution has a publication fund made possible by the contributions of a generous friend. It is to be hoped that the next report contains papers showing more of a research spirit.

S.

THE COLLOIDAL STATE IN ITS MEDICAL AND PHYSIOLOGICAL ASPECTS By SIR WILLIAM M. BAYLISS, F.R.S., M.A., D.Sc., LL.D., Professor of General Physiology in University College, London. Pp. 95; 12 figures. London: Henry Frowde, Hodder & Stoughton, 1923.

THIS monograph is to be regarded as an attempt to give a short account of the properties of colloids, so far as of interest in connection with the phenomena occurring in living beings. The nine chapters discuss; (1) the nature of the colloidal state; (2) interfacial phenomena; (3) precipitation and peptonization: (4) osmotic pressure; (5) viscosity; (6) surface tension of colloidal solutions; (7) imbibition; (8) physiological action; (9) proteins and hemoglobin. Although the form of the booklet necessitates rigorous selection of topics, the author finds space to explain his individual views on the colloidal state and to express his disagreement with Jacques Loeb on more than one detail. To the rapidly growing group of medical men who feel the need of greater familiarity with adsorption, the

isoelectric point, amphoteric electrolytes, the Donnan equilibrium and kindred topics, this timely and relatively simple presentation by a master of the subject will be most welcome. K.

UEBER DIE PATHOLOGISCHE ANATOMIE DER SPIROCHÆTOSIS ICTERO-HÆMORRHAGICA INADA (WEILSCHE KRANKHEIT). By PROF. DR. RENJIRO KANEKO, a.o. Professor I. med. Klinik der Kyushu Imperial Universität, Japan. Pp. 182; 12 illustrations and numerous tables. Vienna: Rikola Verlag, 1922.

A THOROUGH systematized inquiry into the morbid anatomy of the Japanese form of this disease, written in the manner of the previous generation, now unfortunately rare, and based on eight years personal observations of cases, of which 42 had come to autopsy. Coupled with a fifty page critical review of the literature, this book is a valuable contribution to the subject; though the reader must remember that the European form of the disease is not identical and that still another epidemic jaundice has recently been shown to exist in this country. K.

THE PRACTICE OF MEDICINE IN THE TROPICS. Volume III. By many authorities. Edited by W. BYAM, O.B.E., Lieut.-Colonel, Royal Army Medical Corps (retired); Lecturer on Tropical Medicine at St. George's Hospital Medical School; late Assistant Director of Pathology, London District; and R. B. ARCHIBALD, D.S.O., M.D., Edinburgh; Major, Royal Army Medical Corps (retired); Director of the Wellcome Tropical Research Laboratories, Soudan Government, Gordon College, Khartoum. Pp. 865; 32 illustrations. London: Oxford Medical Publications, 1923.

THE third volume of Byam and Archibald's practice of tropical medicine is preceded by a very splendid likeness of the late General Gorgas, a particularly appropriate and a very agreeable courtesy from our English colleagues. This volume takes up in detail the diseases produced by intestinal parasites, diseases caused by physical agents, diseases of doubtful causation, some of which are present in the temperate climate, as for example rabies and smallpox. These sections are then followed by disorders of metabolism as seen in the tropics including the deficiency diseases. Regional diseases are considered in another section, a section on surgery in the tropics and a rather unusual section on diseases of women in the tropics.

The sections, as in the previous two volumes, are extremely complete and very thorough, and are presented by well-known authorities. It is interesting to note the opinion of the authors as to the etiology of some of the disorders which are at present in question. Pellagra is considered to be the result of a possible inherited predisposition with continued dietetic deficiency. Typhus fever is classified in the doubtful diseases and possibly, although the authors of the section on typhus fever do not believe it, due to the Rickettsia protazeki. The same thing holds good for Rocky Mountain spotted fever and trench fever. The last two diseases are probably due to the Rickettsia bodies.

The third volume completes this monumental work in tropical diseases and undoubtedly this present publication will stand for many years as the recognized authority on these various manifestations of disease which are observed chiefly in the tropics. M.

THE BACTERIOPHAGE—ITS ROLE IN IMMUNITY. By F. D'HERELLE, Pasteur Institute. Authorized English Translation by GEORGE H. SMITH, Assistant Professor of Bacteriology, Yale University. First edition. Pp. 282; 14 illustrations. Baltimore: Williams and Wilkins Company, 1923.

THE book consists of two parts. Part I deals with the methods of isolation and the demonstration of the Bacteriophage. Part II discusses its importance in disease and its role in immunity. D'Herelle gives the student the benefit of his extensive researches. His conclusions as to the nature, the role in disease and immunity are often at variance with those of other investigators; however the author takes great pains in answering criticism, in an effort to prove his theories. The problem is one of great experimental interest, but the author is undoubtedly overestimating its ultimate value.

P.

ENVIRONMENT AND RESISTANCE IN TUBERCULOSIS. By ALLEN K. KRAUSE, A.M., M.D., Associate Professor in Medicine, Johns Hopkins University; Director, Dows Tuberculosis Research Fund, Johns Hopkins University; Editor, American Review of Tuberculosis. Pp. 137. Baltimore: Williams and Wilkins Company, 1923.

THESE two essays by an author of recognized authority will interest those seeking more light upon the mechanism of resistance to tuberculosis. The formation of the tubercle, its chance position,

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THESE two essays by an author of recognized authority will interest those seeking more light upon the mechanism of resistance to tuberculosis. The formation of the tubercle, its chance position,

its age and vascular supply, the part played by trauma, strain, intercurrent infections, and finally allergy, are all discussed in a masterly fashion. A.

MASSAGE AND MEDICAL GYMNASTICS. By DR. EMIL A. G. KLEEN. Second edition. Pp. 564; 182 illustrations. New York City: William Wood & Co.

THIS book of Dr. Kleen's has been a guide for doctors, medical students, masseurs and medical gymnasts in Scandinavia for more than a quarter of a century. The original edition appeared over twenty years ago and so well satisfied has the author been with its original contents that he has found no reason for making any material alteration in the present edition. The present volume contains a chapter on Ling's Medical Gymnastics by Dr. J. Arvedson, a chapter by Dr. E. Zander on Zander's Medical Gymnastics and another chapter by Dr. Patrik Haglund on the use of Medical Gymnastics and Massage in Orthopedics.

This book, coming as it does from Sweden, where methods of massage and gymnastics have received scientific thought for the last hundred years, makes it a book well worth investigation for those who are laboring in this field. In includes a most interesting historical introduction which goes to show that massage and physical exercise have formed a branch in medical and surgical treatment from time immemorial in all countries. Naturally, some of the authors views receive criticism when read by English-speaking people. This does, by no means, miminize the value of the book. The illustrations are somewhat antiquated, although they serve the purpose quite satisfactorily. The important thing in the reviewer's mind concerning such a book as this one, is that it calls increasing attention to the value of physical methods of treatment. The need for such a knowledge was demonstrated anew in the work of recent war surgery. There is no doubt that too little attention is paid to this branch of therapeutics by the average medical curriculum. S.

FOOD AND THE PRINCIPLES OF DIETETICS. By ROBERT HUTCHINSON, M.D., EDIN., F.R.C.P., Physician to the London Hospital, and to the Hospital for Sick Children, Great Ormond Street. Fifth edition. Pp. 610; 33 diagrams and 3 plates. New York: William Wood & Co., 1922.

THIS is an ably written and rather comprehensive text-book, the original edition of which appeared in 1900. While obviously some

attempt has been made to bring the present edition abreast of the times the impression one gets in reviewing it is that it represents in the main the state of knowledge of dietetics a decade or two ago. Many of the references, and they are quite profuse for a book of this kind, date back into the Nineteenth Century and the food prices quoted are those of prewar days. In spite of this defect the work is a most satisfying one, presenting the principles of dietetics in a rational and most convincing manner, and a careful perusal of it will repay anyone. M.

CANCER AND ITS NON-SURGICAL TREATMENT. By L. DUNCAN BULKLEY, A.M., M.D., Senior Physician to the New York Skin and Cancer Hospital, Member of the American Association for Cancer Research. Pp. 457. New York: William Wood & Co.

THE surgical aspects of cancer have so monopolized the clinical literature on cancer in recent years that it is very refreshing to come across a book that deals solely with the medical features. Bulkley has aimed, as he states in the preface, to establish on firm scientific grounds the proofs of the constitutional nature of the disease and to illustrate the value of this thesis by cases, in many of which he has obtained quite remarkable results by purely medical treatment. He does not believe in the local nature of the affection, looking upon the tumor itself merely as a manifestation of a general disease, carcinosis. In his analysis of known clinical and experimental facts he presents a strong case for his theory, which after all is not new though much neglected of late. M.

ABDOMINAL PAIN. By PROF. DR. NORBERT ORTNER, Chief of the Second Medical Clinic at the University of Vienna, Authorized Translation by WILLIAM A. BRAMS, M.D., Formerly Lieutenant-Commander, Medical Corps, U. S. N., and DR. ALFRED P. LUGER, First Assistant, Second Medical Clinic, University of Vienna. Pp. 362. New York: Rebman Company, 1922.

THIS is an English translation of the second and latest edition of Ortner's well known work on Abdominal Pain. In the author's preface to this American edition he expresses the hope that it will be a means of helping in reëstablishing friendly relations between members of the medical profession of the English-speaking countries and of his own. It is very evident that he has in mind the propaganda for the restoration of Vienna to its prewar status as a post-

graduate medical center. The war has undoubtedly demonstrated for us, at least, that American centers afford just as good opportunities for study and that the European doctor is in no respect our superior. Medicine should, of course, know no nationality, but it is rather difficult to forget the attitude taken by some of the central power scientists prior to and during the war.

The present edition is arranged much as was the previous German edition and takes up the subject from every angle. Diffuse and localized abdominal pain, epigastralgia or stomach cramps, pains in all of the abdominal regions and pains associated with various phenomena are taken up in the different chapter headings. In the lines of the book, the author sets forth his own wide personal experience, one based upon the verification of clinical observation by surgical and anatomical check-up.

The impression that one quickly recieves in reading the book is that its author has a profound and extensive insight into his field. Often one wishes that he had not been so concise. The effect is much as though one were seeing a country from a swiftly moving express train.

Somehow or other the style fails to drive home the subject-matter. The topic of abdominal pain is, of course, a large, difficult and intricate one to handle and we know of no one who has presented the case in a better way. Perhaps the fact that we are dealing with a translation accounts for some of our objections.

As for the facts as they are thrown on the screen, no objection could be made against them. We were interested in the terms liver colic, hysterical fever and the evident importance attached to the Abderhalden reaction in pregnancy. The book deserves the attention of all who may be interested in medicine and more particularly internal medicine. It has much of value crowded between its covers.

S.

THE SPECTROSCOPE AND ITS USES IN GENERAL ANALYTICAL CHEMISTRY. By T. THORNE BAKER, A.M.I.E.E., F.R.P.S. (author of Radiographic Technic). Second edition. Pp. 208; 98 illustrations. New York: William Wood & Co., 1923.

THIS small book, which first appeared in 1907, was written to fill an intermediate position between the ordinary text-book of physics and advanced works on the spectroscope. Of the ten chapters into which it is divided the medical man will find the first three the most useful. Such subjects as spectrophotography and spectrophotometry, fluorescence, phosphorescence and calorescence are taken up in the later chapters, with a final one on roentgen-ray spectral analysis.

K.

CONTRIBUTION A L'ÉTUDE DES MANIFESTATIONS TARDIVES DE L'ÉNCÉPHALITE EPIDÉMIQUE. By GABRIELLE LÉVY (Service du Professeur Pierre Marie). Pp. 312; 57 illustrations: Paris: Vigot Frères, 1922.

THIS book is the result of intensive study of 129 cases in the clinic of Professor Marie of the results that may follow an acute attack of epidemic encephalitis. It is well brought out that the severity of the acute symptoms bear no relation to the results that may follow. The sequelæ in the order of their importance are: (1) The Parkinsonian syndrome (which the author very carefully differentiates from Parkinson's disease); (2) the excito-motor syndrome, including the choreas and all other types of involuntary movements; (3) the insomnia and hypomanic forms which occur especially in children; (4) the respiratory form. The histories of 68 cases are given in detail. The pathology of 4 cases is gone into and the literature reviewed. In 1 case there was a persistence of the acute changes which is interpreted as pointing to the virus persisting. It is a very readable book and is an important contribution to our knowledge of what may happen to a patient who recovers from acute epidemic encephalitis. W.

THE SUCCESSFUL PHYSICIAN. By VERLIN C. THOMAS, M.D., Visiting Physician to Franklin Hospital, San Francisco. Pp. 303. Philadelphia and London: W. B. Saunders Company, 1923.

To those physicians who believe that their success depends primarily upon the amount of money they accumulate, this book will greatly appeal, for it discusses the various aspects of their life from that angle. This includes methods of attracting and holding patients, of becoming favorably known in one's community and of changing ability into income. The book also includes chapters on personality, choice of location, forms of practice, accounts, investments, insurance, etc. The opinion is expressed by the author that young men go into this profession essentially for selfish reasons and only incidentally for altruistic ones. And furthermore the author admits that but few doctors are able to put aside enough money for their comfort in old age. The logical conclusion is that physicians are not usually successes. This conclusion is obviously a false one and in itself disproves the author's standard of success. Scattered through the book are some helpful suggestions for the beginner in practice, but much of the advice given is not needed by the graduate of today, and the emphasis placed on material success is unfortunate.

M.

ORTHOPEDIC SURGERY. By SIR ROBERT JONES, K.B.E., C.B., and ROBERT W. LOVETT, M.D., F.A.C.S. Pp. 699; 712 illustrations. New York: William Wood & Co., 1923.

THE hopes aroused by the names of the eminent authors are fully justified by the book. The ever-widening field of orthopedic surgery is exemplified by the range of its contents, which includes almost all diseases of the locomotor apparatus, whether of bone, joint or nerves, except the acute infections and recent fractures. A valuable feature of the book is the introductory remarks on anatomy, functions and general pathology of the parts under consideration, which seek to correlate symptomatology and treatment with general principles of disease and disordered function rather than with each separate entity. This not only aids the memory but helps the student and practitioner to formulate treatment on a rational basis. The book excels in the presentation of those subjects which have long been regarded as the special field of orthopedic surgery, *e. g.*, tuberculosis of the bones and joints, congenital deformities, static and other acquired deformities and principles and details of apparatus, muscle-training, etc. The subjects of bone tumors and malunited fractures are treated less comprehensively, but this can scarcely be regarded as a defect.

Typography, paper and illustrations are excellent. This book is certainly the standard single volume work on orthopedic surgery in the English language. P.

ARAB MEDICINE AND SURGERY; A STUDY OF THE HEALING ART IN ALGERIA. By M. W. HILTON-SIMPSON, B.Sc. (author of *Among the Hill Folk of Algeria*, etc.). Pp. 96; 12 illustrations and 8 plates. London: Oxford University Press, Humphrey Milford, 1922.

OWING to the kindly interest taken in his work by the late Sir William Osler, the author, himself a layman, presents certain very interesting data regarding the present-day medicine and surgery of the practitioners of the remote valleys of the Aures Mountains. He and his wife spent four winters there making an ethnographical survey and were able to get into very close touch with many of the native doctors, learning from them many of their professional secrets. These are presented from the point of view of the native physician and make very entertaining reading. It is exceedingly enlightening to realize that even today, in a French colony, trephining operations are frequently performed with crude red-hot instruments on patients without anesthesia, and that fever is treated by magical observances. M.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

Further Observations on the Roentgen-ray Treatment of Toxic Goiter.—MEANS and HOLMES (*Arch. Int. Med.*, 1923, **31**, 303) start their article by making an announcement of the fact that this is a continuation of some earlier work published in 1917 and again in 1919. The new cases include 44 cases of exophthalmic goiter and 14 cases of toxic adenoma. Later, they plan to report on the cases treated by surgery alone or by surgery and roentgen-ray combined. In the introduction they give the credit to F. H. Williams for first using the rays in exophthalmic goiter. The use of it rapidly spread so that in 1908, Pfahler and Zulick reported upon a large number of cases. At the Massachusetts General Hospital they have a special thyroid clinic and representatives of the medical, surgical and roentgen-ray staff. Each new case is gone over thoroughly by each representative of the special staff. The method of treatment consists of the following details: Acting upon the principle that the effect of radiation will be the greater the larger the amount of radiation absorbed and the more active and less stable the cells composing the gland at the time of exposure, they attempt to obtain the largest possible dose possible without injury to the skin. In general, they find that a reduction of at least 25 per cent of the calculated dose is necessary if reddening and tanning are to be avoided, thus obviating the dangers of atrophy and telangiectasis. They give the treatment approximately every three weeks, but do not continue treatment past a period of five months. Three areas are exposed: One on each side of the neck or thyroid and one over the upper part of the sternum in the region of the thymus. In their recent series of *exophthalmic goiter*, 44 patients in all, 16 showed little or no improvement, 8 of these came to operation later and were

apparently cured. Of the 28 patients listed as improved, 12 were cured and 16 were improved, but were not rendered free from hyperthyroidism. No case seemed to be made worse by the treatment. Two patients that were improved but not cured were later operated upon and 1 of these died. They then illustrate their article with a protocol of every case with a series of illustrative charts, showing how there is usually a decided fall in pulse, basal metabolism and an increase in body weight after roentgen therapy. Five cases with *toxic adenoma* were cured out of 14. They also report on 9 of the 15 patients treated by roentgen-ray previous to 1919. Of the remaining 6, 3 have been lost and 3 have died. Six of the 9 patients have normal metabolic rates five or six years after their first treatment; 1 has a slight elevation without clinical signs. The remaining 2 have elevated metabolism, and clinically were better but not well. They then take up the questions of whether the roentgen-ray itself did any good in toxic goiter, whether it works in all cases, what the manner of its action is and the permanency of the effect. They believe that the roentgen-ray has a decided effect. They discuss Plummer's contention that the natural course of exophthalmic goiter is an uneven one: The patient may get well without treatment. Plummer criticized their previous reports on lack of control patients, and they discuss this and use as an analogy the dietetic treatment of peptic ulcer. Concerning the question of what evidence we have that roentgen-ray is an agent capable of inhibiting or destroying cell function, it has been shown by laboratory investigations that if a living organism be exposed to radiation, retardation of growth, inhibition of function and death to the organism will take place, and that this change will be dependent upon the amount of radiation absorbed, the character of the cells rayed and the conditions to which they are subjected before and after radiation. They also bring out the point that glandular functions are especially sensitive to radiation. About one-fifth of a dose necessary to produce slight reddening of the skin if absorbed by the ovaries will cause cessation of the menses. Similar doses will stop the flow of spermatozoa from the seminal fluid, and a much smaller dose will stop the flow of saliva from the parotid gland. As far as the thyroid goes, it is possible to produce myxedema by the use of the rays. They believe also that in about two-thirds of the cases vigorous roentgen-ray treatment is followed by progressive improvement shown by clinical signs, by behavior of the pulse, metabolism and body weight. This continues for about four or five months and may go on to recovery or may fall short of it. When the latter takes place the treatment seems of little value. In cases that have shown marked improvement and have then relapsed a second course of treatment is indicated. Patients who do not respond to the roentgen-rays in four or five months and those who while improved are not cured should be given the benefit of surgery. They contend that the proper way of using the roentgen-ray in exophthalmic goiter is to give it a fair trial with the idea it may effect a cure, or if it does not, it makes the patient a better operative risk by reducing the degree of hyperthyroidism. In answer to the question why roentgen-ray should be used instead of operation, they say that in operation there is always a certain mortality. Neither method is an ideal method of treatment

and neither attack the cause of the disease. In the matter of toxic adenoma here surgery is decidedly indicated, because the seat of trouble is in the thyroid, and surgery removes the cause, although roentgen-ray gives very decided improvement. The authors discuss the effect of rest also in the treatment of these cases and the removal of focal infection, also the course of pregnancy and cardiac complications. Their conclusions in brief are that roentgen-ray is beneficial in toxic goiters; two thirds of the patients improve; the patients make better operative risks.

Vaccination of Monkeys against Pneumococcus Type I Pneumonia by Means of Intratracheal Injections of Pneumococcus Type I Vaccine.—CECIL and STEPHAN (*Pub. Health Reps.*, Washington, 1922, Reprint 796) have previously attempted to immunize troops against Type I pneumococcus infections by subcutaneous administration of killed pneumococci. In the present paper they report the results of experimental observations on monkeys which they attempted to immunize actively by intratracheal injections and inhalations of killed pneumococci Type I. Striking success followed the intratracheal injections, and this was obtained with smaller doses (one-tenth) than when subcutaneous administration was used. Pneumococcus spray, when inhaled, failed to induce immunity. This is possibly explained by subsequent experiments with India ink which showed that monkeys would allow little or none of the vaporized fluid to enter the trachea, a difficulty which would not be encountered in vaccinating man by the spray method. The authors believe that immunity established by intratracheal injections of pneumococcus vaccine is cellular in character. Little or no protective substance can be demonstrated in the serum of monkeys vaccinated by this method.

Observations on the Role of Cockroaches in Disease.—McFIE (*Ann. Trop. Med. and Parasitol.*, 1922, **16**, 441) in his opening paragraph, remarks, "As the cause of disease and as possible carriers of pathogenic organisms, cockroaches have received less attention than other domestic pests, and less than might have been expected, considering their wide distribution, their abundance especially in tropical countries, their filthy habits and the opportunities they have of contaminating food, and the almost universal loathing with which they are regarded." The author's studies showed that the following organisms appeared to pass unharmed through the intestine of the cockroach (*Periplaneta americana*): *B. tuberculosis*, *B. lepræ*, cysts of *Entameba histolytica*, *E. coli* and of an ameba of a monkey resembling *E. coli*, cysts of *Giardia intestinalis* and eggs of *Ankylostoma duodenale*, *A. braziliense*, *Necator americanus*, *Ascaris lumbricoides*, *Trichuris trichiura*, *Tenia saginata* and *Schistosoma hematobium*. On the other hand, *gonococci*, the vegetative forms of *Entameba histolytica*, *E. coli*, eggs of *Aphiochcta xanthina*, and in two experiments each, *Bacillus typhosus*, *B. paratyphosus* and *B. dysenteriæ* (Flexner Y) were not recovered from the feces of cockroaches after experimental feeding. No evidence was obtained that any of the organisms used in the experiments established themselves as parasites in the intestine of the cockroaches.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Ptosis of Right Colon.—QUAIN (*Arch. Surg.*, 1923, **6**, 638) says that coloptosis is a very common anatomic abnormality. Comparatively few of those who have a ptotic colon suffer serious symptoms. Some of the effects of coloptosis are translated to other abdominal organs, which may then give rise to a new set of symptoms, thus obscuring the original and chief cause of the trouble. Medical treatment gives relief in most cases and should be given a thorough trial in all cases, but its ability to cure is doubtful in any case. Surgical treatment is as successful in these lesions as in many other so-called surgical diseases and promises better results as experience accumulates. Chronic appendicitis is an infrequent disease and the term should be restricted to those comparatively few instances in which there actually is a chronic lesion of the appendix.

Spondylolisthesis.—KLEINBERG (*Ann. Surg.*, 1923, **77**, 49) says that the condition occurs more frequently in males than has been believed heretofore, especially among laborers. Trauma is frequently the direct cause or at least a very important factor in etiology. There is a definite radiographic appearance which is pathognomonic and has not been found or described for any other lesion. The last lumbar is larger than the other vertebræ. The main feature of roentgenogram in the lumbosacral region is the distinct outlining of each lumbar vertebra with the fifth, separated from the sacrum by a definite interval. Therefore, when the superior surface of the last lumbar vertebra is seen while the other vertebræ appear quadrilateral, then a diagnosis of forward dislocation of the last lumbar vertebra is justifiable, while in a clear lateral view the presence of the shadow of the body of the last lumbar in front of instead of above the sacrum makes the diagnosis absolutely positive. This lateral finding is of prime importance.

The Metastasizing Tendency of Esophagus Carcinoma.—HELSLEY (*Ann. Surg.*, 1923, **77**, 272) says that in 70 per cent of carcinoma of the esophagus, metastases were present in 36 per cent. In 6 per cent the secondary growths were limited to the regional lymph nodes. This indicates a limited tendency to metastasize. The average duration of symptoms, 4.8 months in the patients who died without metastases, indicates that in the majority of cases ample time is given for diagnosis and treatment before metastases occur. However, the striking change for the worse in the pathological picture during the average of sixty-

nine days by which the group that survived gastrostomy outlived the group that succumbed thereto gives warning of the speed with which metastases developed in a somewhat advanced stage of the disease. Irrespective of the duration of the disease, the possibility of metastasis formation without definite evidence of the same should not be considered as a contraindication to radical operation.

Primary Carcinoma of Liver.—HELVESTINE (*Jour. Cancer Res.*, 1923, **7**, 209) says primary carcinoma of liver occurs in 0.03 per cent of all necropsies, according to statistics collected by Winternitz. It therefore occurs very rarely in the experience of any single pathologist. The condition is rapidly fatal, for the duration of the disease seldom exceeds three months. Despite its malignancy surgical intervention has met with some success. One author has reported reoperation for recurrence seven years after removal of primary growth. Hepatomata are differentiated from cholangiomata by the arrangement of the cells, the presence of capillary stroma and the absence of proliferation of the bile duct epithelium. Cirrhosis was not present in the case analyzed. The growth was unicentric in origin, the primary focus being in the right lobe, whence it grew by direct extension without using the portal system as a pathway.

Stoffel Operation for Spastic Paralysis.—HEYMAN (*Surg., Gynec. and Obst.*, 1923, **36**, 613) says that from the results obtained by the Stoffel operation in a series of 24 cases the spastic contractures of the adductors and spastic equinus can be absolutely relieved. Only 2 cases of contracture of hamstrings were operated and the evidence is not sufficient for opinion. In one of these, however, recurrence had followed tenotomies, and at present writing, one year after the Stoffel operation, there is no tendency toward contracture; while spastic contracture of the fingers and thumb can be relieved, the ultimate function of the hand is not so encouraging as in the lower extremity. The author believes that the results are due to the extreme complexity of motions acquired in the normal hand.

Renal Function Following Nephrotomy.—MAGOUN (*Surg., Gynec. and Obst.*, 1923, **36**, 675) says that the arrangement of the arteries of the kidney differ in man and dog. Complete nephrotomy bilateral or unilateral may be performed in dogs with maintenance of life and renal function. A single kidney may be subjected to nephrolithotomy and maintain sufficient function to support life and health. Secondary hemorrhage is a real danger in complete section of the kidney. Smaller incisions, single or multiple, may be made into the kidney, to remove stone with small risk of secondary bleeding. Generally, pelviotomy is the operation of choice in the treatment of renal calculi. However, in selected cases nephrolithotomy is indicated.

The Conservation of Muscles in Paralytic Deformities of the Foot.—ROBERTS (*Jour. Bone and Joint Surg.*, 1923, **5**, 123) says that no single muscle of a group supplied by the same terminal nerve is likely to be paralyzed if the other members of the group have regained nearly normal power. Working on this observation the author has devised

very satisfactory treatment in types of valgus deformity in which the tibialis anticus is functionless and in the movement of dorsiflexion the foot is drawn outward by the action of the common extensor in spite of vigorous effort on the part of the extensor hallucis to maintain the median position. The tibialis anticus is apparently paralyzed with the other two of the group supplied by the deep peroneal nerve functioning well. The author suggests the inability of the tibialis anticus to function is due to stretching and the consequent atrophy from disuse. The operative procedure consists essentially of reinforcement of the tibialis anticus. Sixty-six cases so treated show definite return of contractility in the tibialis anticus muscle three months after the splints had been removed.

The Mercury Inhalation Therapy of Syphilis.—GUTMAN (*Am. Jour. Syph.*, 1923, **7**, 145) says that mercury vapor inhalation therapy has been employed very extensively in many countries and for many centuries, that numerous competent physicians in almost all countries and almost all times utilized this therapeutic factor in the cure of syphilis and other diseases. Mercurial vapors when administered in sufficient quantities have never lacked action, always producing results, either desirable or undesirable. Pure metallic mercury was rarely used, but the drug was commonly employed either impure or in chemical combination. Complications are noted most frequently when other substances have been added to the mercurial compounds. Older physicians for one reason or other mixed the mercurial substance with foreign, mostly undesirable ingredients. The vaporization process of mercury mixtures was conducted in a multitude of ways, while the vapor was administered in an indiscriminate manner, and while there is much in the past history of mercury vapor therapy that is unfavorable, there is much more which commends the method and places it among other recognized procedures.

Coxa Plana and its Causation.—JANSEN (*Jour. Bone and Joint Surg.*, 1923, **5**, 265) says that the femoral head and neck, when being deformed to the condition which was first described by Dr. Tagg, passes through several flattening stages, with some fragmentation of its bone center. This final stage is called coxa plana fragmentation. On further growth these fragments reunite to form a wide femoral head in the adult. It is well known that coxa plana is a satellite of congenital dislocation of the hip and reversely. Patients with coxa plana are regularly distinguished from those with *bacterial* inflammations by their healthy appearance, the small amount of pain, the absence of fever and mostly by the absence of reflex stiffness and restriction of movement throughout life. Bacteria cannot explain the thickness of the socket floor or the ischium varum, the horizontal position of the growth disk and the correlation with congenital dislocation of the hip.

Tendon Transplantations for Musculospiral Paralysis.—STEVENSON (*Glasgow Med. Jour.*, 1923, **17**, 225) says that musculospiral paralysis is a comparatively uncommon occurrence in surgical wards of a general hospital, usually occurring with fractures of the upper arm or accidentally during an operation. The author has noted that a clean cut of

the musculospiral which was immediately sutured was followed by a period of inactivity for one year before restoration of voluntary movement in extensor muscles; the alternative operation is tendon transplantation. The technic is described by the author, modifying Stile's original operation. The procedure is constant regarding three tendons. The entire flexor carpi ulnaris is used as the transplant for the extensor communis digitorum, extensor indicis and minimi digiti. Palmarislongus if present is inserted into the radial extensors. Reëducation of the transplanted muscles is invaluable in this stage. Wrist flexion is continued satisfactorily by the action of the flexores sublimis and profundus digitorum.

THERAPEUTICS

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

NEW YORK,

AND

CHARLES C. LIEB, M.D.,

ASSISTANT PROFESSOR OF PHARMACOLOGY, COLUMBIA UNIVERSITY.

Ionic Medication.—The theory of ionic medication was originally enunciated by Verratti in 1747 and was introduced into therapeutics by Lœduc in 1900. The enthusiasm of the proponents of this method of treatment and the vehement condemnation of its opponents led CAMPBELL (*Brit. Med. Jour.*, 1923, **1**, 409) to undertake a critical examination of the whole subject. He concludes, from a considerable number of experiments and clinical observations, that (1) the amount of any drug (iodine, strychnine, pilocarpine, atropine, salicylate) that can be introduced in an ionic state into the body by electric currents which can be used therapeutically is very small. (2) The drug, as soon as it is carried through the skin, is swept away in the blood stream and produces its usual specific effects on the system generally. There is no local concentration. (3) There is no evidence of deep penetration; all the evidence is against the drug's penetrating farther than the subcutaneous tissue. (4) There is no evidence in support of the claim that in the process of ionization chemical changes are set up in the tissues and that the resultant modification of the chemical constitution of the body produces a therapeutic effect. (5) The temporary alleviation of pain often found after ionic medication is the result of a counter-irritant action. Campbell believes that there is little scientific foundation for the theory or practice of ionic medication.

Rheumatoid Arthritis Treated with Intravenous Bacillus Coli Vaccine.—PERKINS and WHITE (*Brit. Med. Jour.*, 1923, **1**, 411) define rheumatoid arthritis as that type of chronic arthritis attacking the smaller and larger joints and characterized by proliferative changes in the ligaments and effusion into the joint cavities and going on to anky-

losis. This disease is considered an infectious one, though the foci of infection are usually very difficult to find; the commoner foci are the tonsils, alimentary tract and, especially in women, the genito-urinary tract. The treatment is divided into (1) elimination of focus of infection, (2) increase of resistance of the patient to the infection, (3) local treatment to the joint with the objects of (*a*) preventing deformity, (*b*) alleviating pain, (*c*) preserving movement of the joint. In the cases reported in the paper under discussion, careful examination failed to reveal any infected area; it was accordingly impossible to prepare an autogenous vaccine. The authors selected B. coli vaccine because it was readily obtained and easily administered. The normal defences of the patient suffering from rheumatoid arthritis are low and the object of the protein shock is to make a sudden call upon them with the idea of arousing them from their apathy. The vaccine was administered intravenously, the first dose varying from 50 to 200 million. A certain amount of difficulty was experienced in selecting a suitable initial dose; it should be large enough to produce a distinct reaction but not so large as to produce harmful effects. The reaction consists of a rise in temperature to 100 to 103° F., often accompanied by a chill, nausea and vomiting. The duration of the reaction varies from twelve hours to two days and during it the patient should remain in bed. If any improvement is to follow, it usually does so within two days but may not appear for three weeks. The shock treatment is advised in those cases in which no focus of infection can be found and in which the recognized methods of treatment have failed, and in early cases in which the processes in the joints are still active, especially if swelling and effusion are present.

Observations on the Cause and Cure of Chronic Rheumatism.—Harding-Freeland (*Brit. Med. Jour.*, 1923, **1**, 281) defines rheumatism as an acute, subacute or chronic disease due to the invasion of the parts affected by a specific microbe, *Streptococcus rheumaticus* of Pointon and Paine. The treatment recommended is best summed up in the words of the author, "Experience . . . has led me to regard vaccine treatment as essential and other remedial measures as subsidiary, but by no means as unimportant, seeing that, in the vast majority of cases, they are usually desirable and often necessary." Of the 112 cases reported only 17 per cent failed to be improved by vaccine treatment; the cases "cured or markedly improved" number 93 and were distributed as follows: Articular rheumatism (arthritis) 52 cases, with 85 per cent "cured or markedly relieved"; muscular rheumatism (lumbago, etc.) 24 cases, 83 per cent greatly benefited or cured; neural rheumatism (sciatica, etc.) 20 cases, 75 per cent cured or markedly relieved; pharyngeal rheumatism (tonsillitis) 12 cases, all cured or markedly improved; cerebral rheumatism (chorea) 4 cases, all of which were cured and free from symptoms at the end of one year.

The Scientific Basis for Non-specific Protein Therapy.—In this paper Clark (*Brit. Med. Jour.*, 1923, **1**, 315) collects the available scientific evidence showing the nature of the effects produced by non-specific protein therapy. This method of treatment was developed along purely empiric lines and there soon appeared a strong prejudice in favor of the view that such treatment in order to be effective must be specific. It was early discovered that in many cases non-specific vac-

cines and sera were as specific as vaccines and that a large assortment of proteins and protein breakdown products produced the same effects as vaccines. Non-specific protein therapy has been recommended for the majority of known diseases but is of demonstrated value in relatively few. It yields good results in acute general infections such as typhoid fever, where after an exacerbation of the fever it frequently causes termination by crisis; the treatment is also successful in chronic infections, with local lesions in which the injection causes a febrile reaction followed by general improvement in well-being. The local lesions become acutely inflamed during the fever but subsequently heal quite rapidly. Non-specific protein therapy is also valuable in the treatment of acute and chronic arthritis, gonorrhea and anthrax. The injection of proteins, products of protein breakdown and the rapid destruction of body cells all produce a similar reaction; it is probable that they all have a common active principle, namely, a product of protein decomposition. Proteoses and albumoses are very toxic while peptones have a much less poisonous action. The effects of commercial peptone, protein poison and histamine are similar and resemble anaphylactic shock. It is difficult to understand why such a reaction should be of therapeutic benefit. There is no doubt that an excess of protein breakdown products is intensely toxic; traumatic shock appears to be due to protein breakdown products and the toxemia of intestinal obstruction is ascribed to the absorption of proteoses. In employing products in therapy it is essential that the doses be properly graded, for an overdose is extremely dangerous both in its immediate and ultimate effects. The reaction is of benefit only if it is of a certain intensity. The most important effects of protein therapy seems to be a change in the permeability of the capillaries; this is first increased and subsequently decreased. The former leads to an increased flow of lymph which washes into the blood stream a large variety of the products of cell metabolism. The blood changes following protein injection are immediate leukopenia followed by leukocytosis, an increase in the number of young and atypical red blood cells and an increase in the number of platelets; there is also an increase in fibrinogen, globulin, thrombokinase, blood sugar, non-protein blood nitrogen, proteoclastic ferments and antibodies. It appears, therefore, that non-specific protein therapy causes a washing out of the tissue fluids into the blood, resulting in important changes in the composition of the latter. Which of these changes is of primary clinical import remains to be determined.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

Nasal Diphtheria.—IAMS (*Atlantic Med. Jour.*, 1923, **26**, 448) points out that primary infection of the nasal mucosa with the diphtheria

bacillus is not infrequent. It is often exceedingly mild and is not diagnosed because the possibility of its presence is not recognized. The symptoms as outlined in the average text-book, with the exception of the nasal discharge, either do not appear at all or are late symptoms, and are evident only after some days. The theory as to the extreme toxicity of this type was derived largely from the fact that only advanced and serious cases were diagnosed. The mortality is at least no higher than in the faucial type if sufficient antitoxin is given. All severe cases of rhinitis, particularly if unilateral, should be cultured. Many unexplained infections occur and can only be cleared up when the importance of nasal as well as faucial cultures is recognized. As so many cases are not diagnosed, epidemics are bound to occur, and the prevention of these can only be secured by cultures from the nose as well as from the throat.

Osteomyelitis of the Ilium in Children.—BEARSE (*Jour. Am. Med. Assn.*, 1923, **80**, 991) says that the cause of osteomyelitis in the ilium are the same as in osteomyelitis of other bones. The systemic manifestations are also the same, but the local symptoms are likely to be deceptive in that they are usually referred to the hip joints and not to the ilium. The diagnosis is made on the localized tenderness in the acute cases and on the swelling in the chronic cases, and there may be spasm of the muscles of that buttock and below it. There are pain and spasm in that hip on attempted motion, but with care motion can be obtained. The roentgen-ray is a decided aid in old cases, while in acute cases it may show nothing. Stereoscopic plates may help, but once the disease is localized the roentgen-ray is an aid in watching the progress of the disease. The course of the disease in the ilium is similar to that in the flat bones. It is evident that in infection of a flat bone with a thin cortex there will be early perforation, and if the disease progresses, there will be extension of this perforation or a new perforation will appear nearby. By roentgen-ray this is first evidenced by a punched-out appearance or rarefaction which may gradually increase in size. In advanced cases where there are several perforations the bone may take on the appearance of being mottled or moth-eaten. Complications are frequent. Some of these are dislocation of the head of the femur because of erosion of the acetabulum, metastatic infections of other bones, amyloid liver, arthritis of the hip, erosion of the femoral artery, phlebitis of the iliac vein and the development of pus pockets. The treatment is based on general surgical principles and varies with the conditions found. Briefly it is early operation with adequate drainage and removal of dead bone up to resection of the entire ilium.

Dietary Consideration in Infantile Eczema.—GERSTLEY (*Jour. Am. Med. Assn.*, 1923, **80**, 1141) has found that eczema develops in those who are overweight and underweight as well as in those with an adenopathy and also in those without, in those with flabby subcutaneous tissue and also in those with firm subcutaneous tissue. A characteristic common to most, namely, blue eyes, blonde hair and skin of very fine delicate

texture, can be attributed to a simple deficiency of pigment. He outlines a prophylactic treatment. He brings the skin of the predisposed fair-haired, blue-eyed children to the best possible state of nutrition. Irritants at times bring hyperemia and papule formation to sensitive cheeks, but the application of a mild protective salve of any sort, such as cold cream, is sufficient to prevent spreading of the process. If the diet is absolutely unchanged, these findings soon disappear. They may reappear again at intervals but rarely become very marked. If the skin of an infant is maintained in a state of good nutrition from the time of birth and at the same time protected from irritants, eczemas rarely appear. The active dietetic treatment from the standpoint of the pediatrician is that which brings the child most rapidly to the best possible state of nutrition. No one particular diet helps and no one particular diet does harm. The main consideration is to place the welfare of the entire body above the welfare of an individual organ. If this is carried out, local symptoms gradually disappear in proportion to improvement in the general condition. There are only two indications for restriction of the diet. The first is in an overfed baby with an oozing eczema, in which case reduction of food intake is of value. The other is in an infant in whom the eczema has become secondarily infected. A temporary reduction in diet by depleting the tissues of fluid, dries the cheeks and leaves a field less fertile for bacterial growth. In these instances there is no special indication for restricting any particular element of food. Restriction in quantity is all that is necessary.

A Statistical Study of the Tuberculin Test in Infancy and Early Childhood.—WAHL and GERSTENBERGER (*Arch. Pediat.*, 1923, **40**, 143) report a study of the tuberculin test performed upon exposed, suspicious or actively tuberculous individuals of those applying to the Babies' Hospital of Cleveland from 1907 to 1921. They found that a slight increase of the positive tests in the females over the males, the former giving a positive percentage of 61 per cent and the latter a positive percentage of 54. There was an increase in the percentage of positive reactions corresponding with the increase in age, being 35 per cent in infants under six months and 87 per cent in young children between thirty-six and forty-eight months of age. Of the different races and nationalities the colored race gave the highest percentage of positive reactions. Patients exposed to two or more sources of tuberculous infection showed a higher percentage of positive reactions than those exposed to only one. When only one source of contact existed for a patient, the mother was found responsible for the highest percentage of positive reactions, a brother or sister for the next highest and the father for the lowest of the group. Children giving a negative history of exposure showed only 15 per cent of positive reactions as against 44 per cent for those having a positive contact. In other words, 44 per cent of the children giving positive tuberculin tests gave a definite history of the tuberculous contact, while of those giving a negative history of exposure only 15 per cent reacted positively. Scrofula gave the highest percentage of positive reactions and was followed by pulmonary tuberculosis, tuberculous adenitis, tuberculous osteomyelitis,

tuberculous meningitis and pulmonary miliary tuberculosis. By using the intracutaneous test, controlled by checking with a known case of tuberculosis, a higher percentage of positive reactions can be obtained, especially in cases of tuberculous meningitis and pulmonary miliary tuberculosis than has been usually reported. The intracutaneous test, 0.1 cc of a 1 to 100 solution, is in practically 100 per cent of the cases more sensitive in its reaction than the tuberculin tests performed either by the tattoo or the burr method. In the same way the test performed by the tattoo method is more sensitive than by the burr method, although the first is more difficult from a technical standpoint. The intracutaneous test with a 1 to 1000 solution has always been found positive even when stronger dilutions of 1 to 10 or 1 to 100 were used. The reactions with the stronger solutions have been in general more marked, but the reaction with the 1 to 1000 dilution has been sufficient to convince the authors to choose it as their standard in performing the intracutaneous test.

Brain Tumors in Young Children.—Wollstein and Bartlett (*Am. Jour. Dis. Child.*, 1923, **25**, 257) in 7 cases of tumor of the brain in children between the ages of two weeks and three years found that the average age was fifteen months. All of these tumors were gliomatous in type. Two were supratentorial and five were infratentorial. Of the supratentorial tumors, one occupied the left cerebral hemisphere and was congenital in origin. The other occupied the basal ganglia. In the 5 infratentorial tumors the vermis of the cerebellum was involved. The growth involved the right cerebellar hemisphere in four and the left hemisphere in only one instance. The medulla and the pons were infiltrated in 2 cases and the right cerebellopontile peduncle was involved in 2 instances. The upper cervical cord was compressed in 3 of the cases. Hydrocephalus was present in all of the 7 cases. The most striking feature of the symptomatology was the variability in the physical signs. Convulsions were absent in all cases except one in which a convulsion occurred just before death. Vomiting did not appear as a significant symptom in any of the cases. The spinal fluids showed nothing that was distinctive. Xanthochromia was present in only 1 case in which there was a cerebral hernia.

The Characteristics of the Cerebrospinal Fluid in Postdiphtheritic Paralysis.—Regan, Regan and Wilson (*Am. Jour. Dis. Child.*, 1923, **25**, 284) carried out a study of the rachidian liquid to determine whether a meningeal reaction occurred in the spinal fluid in postdiphtheritic paralysis and to assist in establishing the cytological and chemical formula in that disease. A series of 28 specimens of spinal fluid from 16 patients were examined at various intervals from the second day to the eleventh week of the paralysis, 22 being in the first four weeks. Nearly two-thirds of the patients had extensive generalized paralysis and in 5 death occurred. These paralyses followed usually a moderately or very severe initial angina, commonly of a polymicrobian or septic form, with extensive membrane formation and frequently accompanied by myocarditis. They draw conclusions from the findings in this

series combined with those of a former series. They found that the cerebrospinal fluid in postdiphtheritic paralysis is a clear limpid fluid flowing usually under normal or slight hypertension. The Bordet-Wassermann reaction of the spinal fluid was uniformly negative in each case. The cell count was always within the normal limits, less than 10 cells per c.mm., and the cells found were small lymphocytes. The globulin was increased in a minor proportion of the patients, less than one-third. The increase was slight, occasionally moderate and never marked. There existed in certain cases less than one-third, a dissociation between the cytological and chemical findings. The colloidal gold reaction was the most constantly positive pathological reaction encountered in the fluid in this disease. The reduction usually occurred in the syphilitic zone, occasionally extending into the higher dilutions. The reaction seemed gradually to subside, reaching normal as convalescence was established and paralysis disappeared.

Transfusion through the Umbilical Vein in Hemorrhage of the Newborn: Report of a Case.—SIDBURY (*Am. Jour. Dis. Child.*, 1923, **25**, 290) remarks that the obtaining of blood from one of the superficial veins of the newborn infant is often a difficult task and is at times even impossible in the hands of an expert. The easiest route is by way of the superior longitudinal sinus, but this route should only be employed by one familiar with its use; but even the experienced worker may fail to enter the sinus because of its distortion from its usual location as a result of molding of the head. This is especially true during the first few days of life. So far as the author knows this method has never been used before, but it appealed to him as a rational method, for the baby had been receiving blood and nourishment through the umbilical vein up until three days previously. The umbilical vein was patent and accessible for transfusion up to and including the fourth day of life. It is up to the fourth day of life the most accessible vein, in a newborn baby, if patent. The probability of a clot in the umbilical vein is very unlikely because the blood is fluid many hours after death in these cases. Transfusion through the sinus in cases of intracranial hemorrhage may increase intracranial pressure, which is not desirable. Transfusion through the superior longitudinal sinus is comparatively simple for one experienced, while the umbilical route is simple enough for those inexperienced in the sinus route. In the case reported 100 cc of blood was introduced through the umbilical vein. In doing this the cord was cut just proximal to where it had been originally ligated. A regular transfusion needle was introduced into the lumen of the largest of the three vessels that were present. This was the umbilical vein. A ligature held the needle in place. First 20 cc of physiological salt solution was injected slowly. The mother was the donor, and five injections of 20 cc syringefuls of the untreated blood of the mother were injected, after which 10 cc of physiological salt solution was added to clear the needle and the vein of blood. After the withdrawal of the needle the stump was tied off as before. There was marked improvement after the injection, and there was a slight febrile reaction following it.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

JOHN H. STOKES, M.D.,

MAYO CLINIC, ROCHESTER, MINN.

Sodium Thiosulphate.—McBride and Dennie (*Arch. f. Dermat. u. Syph.*, 1923, **7**, 63) report upon the use of sodium thiosulphate in the treatment of arsenical and other heavy metal poisonings, with special reference to the use of this drug in arsphenamine dermatitis. The chemically pure preparation may be given intravenously in doses up to 2 gm. without toxic effect. The action depends upon the sulphur content of the drug and is in keeping with the familiar practice of using sulphur derivatives, such as calcium sulphite in the treatment of heavy metal poisoning. Immediately upon the appearance of the arsphenamine dermatitis, doses of 0.3, 0.45, 0.6, 0.9, 1.2 and 1.8 gm. were given on as many successive days. It is possible to give a larger dose at the outset without ill effect. A number of case reports, showing the results of this mode of treatment, are given.

The Course of Syphilitic Infection in Pregnant Women.—Moore (*Johns Hopkins Hosp. Bull.*, 1923, **34**, 89) discusses the results of the survey of 178 pregnant women with positive blood Wassermann reaction and 22 non-pregnant mothers of syphilitic children. Of his series, 22 per cent had outspoken lesions of early or late syphilis at the time of admission. Of the remainder, in only 21.5 per cent were all evidences of syphilis except the positive blood Wassermann reaction lacking. The author feels that he has confirmed and amplified Hutchinson's clinical observations in 1876, which led him to the conclusion that all mothers of syphilitic children are themselves syphilitic and that suppression of syphilis by pregnancy and distortion of the usual time relations of the disease by pregnancy, is an established fact. If impregnation and infection approximately coincide, or if the infection occurs during the course of pregnancy, early but apparently mild manifestations of syphilis may develop. Approximately one-half of the patients thus infected exhibited a reduction in severity of the manifestations of the disease. A slightly larger proportion, infected with syphilis at about the time of impregnation, failed to develop any of the usual early lesions of syphilis. In occasional cases, the usual time relations between primary and secondary syphilis are much prolonged; on the other hand, the interval between early syphilis and tertiary syphilis may be much shortened, and grave lesions of a tertiary type may occur early in the course of the disease. The protection against the early lesions of syphilis afforded by pregnancy may persist over a long period of years and possibly a lifetime. Spontaneous cure of syphilis seems in a few instances to have been the ultimate result. Those women of the author's series who developed late syphilis were especially prone to syphilis of the viscera and of

the cardiovascular apparatus, whereas tertiary lesions of the skin and bones and neurosyphilis, either clinical or symptomatic, were rare. In 33 of the 200 patients, the blood Wassermann reaction gave fluctuating and anomalous results. In 10 per cent of the pregnant women with secondary syphilis, the reaction was negative. A negative or a positive reaction during pregnancy may be spontaneously reversed after the birth of the child. In 2 instances, it was suggested that this variability in the Wassermann may be due to an excess of native amboceptor in the blood in certain women during pregnancy. It was observed that the ice-box Wassermann may be strongly positive when the water-bath test is negative. In another survey, the author found that the incidence of abnormal spinal fluids in women with late syphilis was twice as high in a group of sterile women as in a similar group in which one or more pregnancies had occurred since infection. The mechanism of suppression in the pregnant woman is still undetermined.

Prophylactic Treatment of Syphilis.—Nichols and Walker (*Jour. Exper. Med.*, 1923, **37**, 525) report the results of experimental observations on prophylactic treatment in syphilis. The authors' work is of special interest because of their discussion of the significance of the natural spirochetosis of rabbits (infection with *Spirochetæ cuniculi*) on the experimental study of syphilis in rabbits (infection with *Spirochetæ pallida*). The authors conclude that rabbit spirochetosis does not give rise to a positive Wassermann reaction, while human syphilis in rabbits sometimes gives rise to a positive Wassermann reaction. The course of the lesions on the scrotum and genitalia in natural spirochetosis differs from that in syphilis, and the authors believe a morphological differentiation is possible. The principal purpose of the work was to demonstrate the complete curability of syphilis in an experimental animal by the use of arsphenamine and the authors assert that complete cure is unquestionably possible with one or several doses of arsphenamine. They do not insist that this constitutes a demonstration of curability in man, but they believe that it indicates that cure is possible with sufficient treatment. In testing the value of calomel prophylaxis, they found that it was effective up to eight hours after inoculation and that the ointment base is a matter of less importance than has been supposed. Gland transfers from animals with positive local inoculation yielded 87.5 per cent of takes. Gland transfers in rabbit spirochetosis were negative. The authors feel that rabbit spirochetosis need cause no more serious errors in the study of experimental syphilis than have been produced by the identification of other acid-fast bacilli in the study of tuberculosis in man. They feel that the effects of rabbit spirochetosis are comparable to those of Vincent's angina in man. In studies of generalized syphilis supposed to involve the genitalia and in sexual transmission experiments, *Spirochetæ cuniculi* may be a serious complicating factor.

The Treatment of General Paresis by Induced Infection with Malaria Plasmodia.—Pilcz (*Lancet*, 1923, **204**, 19) directs attention to and summarizes the results of the treatment of general paresis by induced infection with tertian malaria according to the technic of von Wagner and Gerstmann. The technic, as described, consists in the injection

of 2 cc of blood from a patient with tertian malaria (not tropical malaria), beneath the skin of the paretic patient's back. This blood must be obtained by venipuncture during the attack of fever. After one or two weeks, on an average, the paretic develops his first malarial attack. After some ten or twelve attacks, the malaria is checked by quinine during the first three or four days (0.5 gm. of quinine sulphate twice a day for three or four days and then once daily for two weeks). At the same time, a course of neo-arsphenamine, 0.3 gm. to 0.6 gm., is begun. Acoustic hallucinations and accentuations of other symptoms are occasionally observed during the malarial stage, but disappear promptly when the quinine cure is started. Of 141 paretic patients treated in 1919–1920, 51 have completely recovered, 18 showed marked and persisting remission without being able, however, to return to their former occupations, 57 cases became stationary or showed incomplete remission, and 15 patients died. Simple dementia and the maniacal types show the most favorable prognosis. The development of remission is gradual, and not necessarily parallel in degree or duration with serological reaction. Some good results are claimed in tabes and disseminated sclerosis. Pilcz further emphasizes the fact that in a survey of 5000 soldiers in whom a 5 per cent incidence of paresis was observed, only 1 of the affected patients had ever had a febrile disease, and those who had undergone febrile infections in no case developed paresis. The author suggests that tropical climates and early treatment by induced fever may have some influence on the course of neurosyphilis.

Lacquer Dermatitis.—Pusey (*Arch. Dermat. and Syph.*, 1923, **7**, 91) reports a case of lacquer dermatitis which occurred in a patient whose business consisted in the selling of cheap lacquered Japanese canes carrying small flags. The lacquer employed on these canes is made from the Japanese lacquer tree (Rhus vernicifera), and the dermatitis it produces has been known in Japan and China for more than a thousand years. Toyama's work indicates that the lacquer from jars buried a thousand years has the same irritant properties as the fresh preparation. The condition is rarely recognized in this country. It yields readily to wet dressings of dilute aluminum acetate solution.

The Resistance of Hair to Certain Supposed Growth Stimulants.—Mildred Trotter (*Arch. Dermat. and Syph.*, 1923, **7**, 93) reports a series of investigations of the effect of petrolatum, of sunburn and of shaving upon the growth of hair. The method employed consisted of the measurement of hairs in different regions, hairs being removed by tweezers at various intervals after a single close shave. It was found that the rate of growth of hair was in a measure proportional to its area of cross-section, which was greatest in the axilla and scalp and least upon the arm. The average life of the hair upon the arm or leg is approximately eleven weeks. The popular supposition as to the effect of petrolatum, of sunburn and of shaving in stimulating the growth of hair could not be substantiated, no apparent change in rate of growth resulting from them. All three of these supposed stimulants were given a thorough trial so the results appear reasonably conclusive. No change in the type of hair growth appeared to result from any of the procedures employed.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Cesarean Section for Double Uterus.—SHOEMAKER (*Jour. Am. Med. Assn.*, 1923, **80**, 103) reports the case of a primipara who upon examination was found to be several months pregnant and to have a double uterus, cervix and vagina, with the pregnancy in the left side of the uterus. She had a spontaneous abortion, in the early months. From this she made a good recovery, and afterward menstruated regularly from both uteri. Later she became pregnant in the right uterus, which gradually enlarged; the left remaining as before. The patient's pelvis was flat. During the remaining months she did well and was threatened with an abortion, but hemorrhage stopped with rest in bed. The vaginal septum was so fibrous as to be an obstacle in labor, and it was impossible to tell the thickness of the wall which divided the two uteri. It was feared that the uterus would rupture during labor. An elective section was decided upon, but the patient came into labor several weeks before the time and was brought to hospital. On examination the right uterus completely filled the right flank and right hypochondrium. The left uterus was about the size of an orange. The child was quickly delivered from the pregnant uterus and each half was found to be apparently a separate organ. The tubes were doubled, ligated and cut, and the uterus was closed. The recovery of mother and child was uncomplicated.

Use of Pituitrin in the Third Stage of Labor.—SEIDES (*Surg., Gyn. and Obst.*, January, 1923, p. 108) treated 500 consecutive cases of parturition by giving each 0.55 cc of pituitrin at the beginning of the third stage of labor. Nothing was done to the uterus except to palpate it sufficiently to find whether the placenta had left the uterus. The patient was made to expel it from the vagina by voluntary effort and the medical attendant made some pressure and gave some support to the recti muscles. Among these cases was one of simple retention of the placenta, and three cases where the placenta failed to separate and required manual removal. The contraction of the uterus was well maintained. The loss of blood was very small and involution went on more rapidly than usually. After-pains were less frequent and less severe. The general health of the patients was considerably enhanced. This experience would indicate that such use of pituitrin considerably shortens the third stage of labor, prevents bleeding, lessens blood loss, lessens and shortens the lochial discharge, and has a tendency to do away with manual compression of the uterus and manual expression of the placenta. Involution is better; after-pains are lessened, and the placenta is not so often retained. The writer believes that pituitrin will not cause retention of the placenta, because

it simply increases the normal uterine contractions which are intermittent and does not produce a tetanic condition of the uterine muscle. He believes that many cases of retention of the placenta arise from excessive or improper manipulation of the uterus, and if this can be done away with the placenta will not be retained.

The Anesthetization of Patients for the Classical Cesarean Section.—SPENCER (*Brit. Med. Jour.*, 1922, **2**, 905) described his usage in anesthetizing patients for cesarean section. He wishes to avoid the dangers to the fetus which result in the deep anesthetizing of the mother and he also wishes to spare the mother so much as possible. Whenever an operation is required he insists that a competent anesthetizer, especially trained, should administer the anesthetic. He believes that the disadvantage of ether is the fact that it leads to asphyxia in the infant when given to a surgical degree. Chloroform exerts its influence in such small quantity that surgical anesthesia is not reached, and hence its effect upon the fetus is very little. From his experience, Spencer has been led to omit hypodermic injections before cesarean section and to give the anesthetic to the patient while upon the operating table, and not in an adjoining room. Chloroform is then given and the child is rapidly delivered, usually in thirty or forty seconds from the commencing of the incision, and in his experience always breaths and cries at once. For the remainder of the operation ether is given, usually by the open method. If there is an unusual loss of blood, pituitrin is administered by hypodermic injection. Where the classic cesarean section is done before or soon after the onset of labor, the child is born free from asphyxia and cries at once.

Is Interference Justifiable in Prolonged Labor?—BECK'S (*Am. Jour. Obst. and Gynec.*, 1922, **4**, 623) paper is based upon what he terms a "sense of security" obtained by the use of his two flap low incision cesarean section. If after prolonged labor a patient cannot deliver herself she can safely be delivered, the writer thinks, by this method. During a prolonged labor the patient is given as much rest as possible. Nourishment is administered freely. An abdominal binder is tightly applied so soon as the membranes rupture if the cervix is almost dilated. The patient is urged to make voluntary effort. Liberal doses of morphine are often given, and whenever the character of the contractions shows that the uterus is fatigued, sufficient morphine is given to stop the labor and allow the patient to sleep. In 1138 hospital confinements there were 79 long labors of whom 66 were delivered spontaneously. There were six forceps cases because of marked change in the fetal heart-rate or prolonged second stage. There were two breech extractions and five cesarean sections. These later were done in cases of relative disproportion where engagement failed after a thorough test of labor. The infant mortality was 7.6 per cent. One mother died on the third day after cesarean section. Of the entire series of 1138 deliveries the total infant mortality was 3 per cent, maternal mortality 1 in 569 cases. These results the writer considers satisfactory in comparison with those obtained by interference. For reasons which he does not state he believes that this method calls for considerable courage on the part of the attending obstetrician, and is

accompanied by considerable worry. If the writer has a "sense of security" which he has obtained by the use of his two flap low incision cesarean section, why worry? [REVIEWER].

Is the Usual Method of Preparing Patients for Delivery Beneficial or Necessary?—JOHNSTON and SIDALL (*Am. Jour. Obst. and Gynec.*, 1922, **4**, 645) have studied various types of labor, and compared results, not only of methods of preparation, but also of delivery. The writers believe that many factors play a part in the causation of morbidity in parturition, operative interference doubling the percentage. Regardless of sterile gloves vaginal examination increases the danger to the patient. Catharsis and lacerations of the perineum do not influence the puerperal period. When the membranes rupture prematurely, it is not the length of time the uterus is drained, but other factors which cause morbidity. With a limited number of patients who had no routine preparation, better results were obtained than among those who had. It is suggested that picric acid as an antiseptic is better than iodine and other antiseptics in use. The strength employed is not mentioned.

Rigidity and Stenosis of the Cervix Complicating Labor.—FÜTH (*Zentralbl. f. Gynäk.*, 1922, **46**, 1671) in his practice, observed a boy aged two, who had upon the head an area 2 or 3 cm. wide, white in color and without hair, and resembling a scar, which was two fingers' breadth above the ear. This scar could be pushed over the cranial bone and was adherent in one point near the forehead. Immediately after the birth of the child there had been a very considerable tumor upon the head, which resulted in gangrene of the skin, and from this gangrene had resulted the scar in question. The cause of this scar and gangrene had been birth pressure from the extraordinary rigidity and tightness of the cervix at the time of the child's birth

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Treatment of Uterine Cancer.—Whenever the subject of the treatment of uterine cancer is under discussion, it is noticeable that there is a distinct plane of cleavage between the classical gynecologists and the radiologists, the former preferring operation at any hazard, the latter blinded by the wonderful results which have been accomplished

by radium under proper conditions. The rank outsider, in his search for the latest information, does not know which camp to follow. Under such circumstances, it is a professional blessing that there are a few men who are as well trained on the one side as on the other and whose opinions, therefore, are unbiassed, but based upon actual clinical experience with both methods of treatment. One of the foremost men of this type is SCHMITZ (*Northwest Med.*, 1923, **22**, 77), who divides uterine carcinoma into five groups: Group 1: The *localized* carcinoma; the neoplasm is clearly confined to the uterus after a physical examination. Group 2: The *borderline* carcinoma; it is doubtful after a physical examination whether the neoplasm is still confined to the uterus or has begun to invade the neighboring tissues, organs or regional lymph nodes. Group 3: The clearly *inoperable* carcinoma, in which an invasion of the neighboring tissues and organs or regional lymph nodes can be demonstrated. Group 4: The *advanced* carcinoma characterized by a "frozen pelvis," a marked cachexia or distant metastases. Group 5: The *complicated* carcinoma; the cancer may be limited to the uterus, but grave constitutional diseases exist. A localized cervical carcinoma can be safely eradicated by an abdominal or vaginal panhysterectomy. The abdominal operation is preferable and after opening the abdominal cavity we should proceed at once to the regional lymph nodes and adnexa. If they are found to be infiltrated, it is useless to proceed with the panhysterectomy, but the operation should be simply exploratory. If an abdominal operation is difficult of execution on account of extreme obesity or mild forms of heart and kidney disease, then the vaginal procedure must be chosen, although it is not possible to explore the pelvic organs as satisfactorily as through an abdominal incision. The Wertheim extended radical abdominal panhysterectomy has a high primary operative mortality, varying from 15 to 25 per cent. It is difficult of execution, accidents are frequent, such as vesical fistulæ and injuries to the ureters and rectum. The advantages claimed for it as to permanent cures are lost by the high primary mortality and, therefore, it can never find a place in our clinics. The accidents during the operation, the primary mortality and the percentage of recurrences increase rapidly if we subject borderline cases to surgical eradication. The possibilities of totally eradicating all carcinoma elements are improbable and infinitesimal. Operative procedures applied to such cancers have tended to discredit surgery, consequently the laity and the general practitioner have realized this state of affairs and hesitate to recommend or to resort to surgical treatment, even if the disease could be successfully eradicated thereby. Confidence of the medical profession and the laity in the surgical treatment can only be reëstablished by an honest adherence to the one indication for surgical treatment of cancer of the cervix—it must be clearly localized within the uterus. Carcinomata of Groups 2 to 5, therefore, contraindicate surgical removal. Unfortunately, the number of malignant neoplasms of these groups form the larger percentage of cancers entering our clinics, the percentage being as high as 80 to 90. The success of radiation therapy depends upon the solution of the problem that a dose of rays must be applied to the deeply seated cervical cancer which will kill it without permanently traumatizing the neighboring healthy tissues and organs, as the bladder, the rec-

tum and bowels. This can be accomplished by the newer technic of radiation therapy for deeply seated malignancies. Of 109 cervical cancers which the author treated between 1914 and 1917, 12 are alive and well. If we subtract the recurrent cases that were operated upon and later on came for treatment of recurrence, namely 31, and the advanced cases, numbering 19, which are treated only palliatively, as they cannot be treated by any known methods of treatment; then there are 59 cases of cervical carcinomata of Groups 1, 2 and 3 with 11 cures, that is, 18.75 per cent. However, if we consider only those cases that possibly would come under the category of surgical statistics, *i. e.*, Groups 1 and 2, we have 14 cases with 6 five-year cures, or 42.85 per cent. Subjecting the statistical results to a minute study, we are at once surprised at the poor results obtained in the last two groups, namely, the advanced and the recurrent cases. Indeed, it is a fact that radiations will cause only a temporary alleviation of the symptoms of the cases in these groups. At times we may observe a case that appears to be subjectively and anatomically relieved, but this relief lasts only for a short while. We also must be careful in the application of the rays in the cases belonging to this group, as otherwise the toxemia caused by the rays may be so severe as to kill the patient. The natural power of resistance to the toxemia is so weakened that the patient can no longer activate sufficient defensive force to tide her safely over the period of reaction. Hence, in this class of cases we attempt to relieve the symptoms by a small dose of radium of about 600 to 1000 mc. hours. Should the regional lymph nodes be involved, and the vaginal fornices and surrounding tissues be free of any recurrence, then the application of a full dose of roentgen-rays is indicated. We often read the statement that, whenever possible, radiation treatment should be combined with surgical procedures, instituted either preceding or following the application of the rays. The author is of the opinion that such procedures do not benefit the patient; on the contrary, she invariably becomes refractory to the rays or has an early recurrence. He also warns against a repetition of the radiation treatment, since, if it has been correctly applied as regards dose and technic, a second application cannot improve the results of the first treatment. The effects of the radiation upon the tissue wear off very slowly, so that from nine to eighteen months pass by before the normal and diseased tissues have completely recovered from the injuries of the first radiation. In answer to the question of whether surgical treatment of a localized cervical carcinoma should be preceded or followed by radiation, the author states that this is unnecessary if the case was truly early and localized. Should the surgeon be in doubt as to the total eradication of the cancer cell elements, then a course of ray treatments should follow, which must be as intense as if the operation had not been performed. The uterine body is replaced by a phantom uterus made of Bakelite, which is inserted between the folds of the broad ligament by removing the row of sutures closing the vaginal roof. Without the use of the phantoms, we cannot apply a dose of gamma rays which would suffice to enhance the action of the roentgen-rays.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Rocky Mountain Spotted Fever: Infectivity of Fasting and Recently Fed Ticks.—SPENCER and PARKER (*Pub. Health Rep.*, 1923, **38**, 333) show the fallacy of depending upon tick-feeding experiments to determine the infectivity of ticks and suggest a combination of feeding and inoculation. Feeding on a healthy animal apparently has the quality of reactivating the dormant virus in an infected tick. It is suggested that the work may explain why so few human infections occur, that is, the ticks may be removed before reactivation. It may also indicate that in time the virus may die out in the ticks.

A Toxin-producing Anaërobe Isolated Principally from Fly Larvæ.—BENGTSON (*Pub. Health Rep.*, 1923, **38**, 340) shows that the botulinus group is made up of at least three types based upon immunity tests, though but two are known to be pathogenic for man; the third probably is toxic for fowls. The cultural and immunological relations do not necessarily run parallel.

The Effect of Vaccinia upon Leprosy.—HASSELTINE (*Pub. Health Rep.*, 1923, **38**, 1) found that in a considerable percentage of cases, lepers reacted to vaccinia by developing a rash in the form of red, infiltrated areas, which declined with the decline of the vaccinia. Desquamation of epidermis followed in some cases. Constitutional symptoms were observed, such as chilliness, fever, malaise. Nodular leprosy and the mixed varieties show the peculiar manifestations, anesthetic cases being little affected.

Eight Years of Epidemic Poliomyelitis in Montana.—SIPPY (*Public Health Rep.*, 1923, **38**, 135) presents the following conclusions based upon eight years' experience: (1) The study of poliomyelitis in Montana indicates that the disease does not originate without previous contact with infected individuals. These infected persons may be only: (*a*) Immune carriers; (*b*) sufferers of mild or abortive attacks; or (*c*) recognized cases. (2) With the exception of a few cases in isolated rural areas, outbreaks tend to occur along principal interstate and intrastate travel routes. (3) Considerable distances between Montana cities afford some natural protection against rapid spread of the disease. (4) Without large, congested population centers, little opportunity is

afforded for acquisition of immunity by contact with mild infections. Rapid spread and a fatality rate higher than usual may ordinarily be expected in isolated communities when infection is introduced. (5) Isolation or quarantine control measures are clearly ineffective without a common knowledge of the importance of recognition of the mild and abortive type cases. (6) The value of antipoliomyelitic serum is regarded as neither proved nor unproved. Its use appears to to be without harmful results, of possible advantage and apparently worthy of further administration and study.

The Trachoma Problem in the State of Minnesota.—CLARK (*Pub. Health Rep.*, 1923, **38**, 383) reports that in 1912–1913, 1 case of trachoma was found to 640 white population and 1 among each 7 of Indian population. The incidence in Indian day schools was 10.48 per cent and in boarding schools 23.86 per cent. In 18 per cent of the cases there was marked injury to vision. In public schools and state institutions the incidence was very low. A more recent survey, December, 1922: Though the figures are not so large, it is believed that the latter survey shows an increased menace in many places and some new foci. In general, it is believed that the disease is fairly well circumscribed. The following recommendations are made: (1) An educational campaign should be inaugurated properly to inform the citizens of the state of the injurious effect of trachoma on vision, its curability and the methods of prevention and control. (2) The regulations of the State Board of Health mandatorily requiring notification of trachoma should be more strictly enforced, and a strong attempt should be made to enlist the coöperation of the physicians of infected districts in detecting existing cases and in eliminating foci of infection. (3) A detailed trachoma survey of the entire Indian population of the state should be made, including isolated Indian bands, for the purpose of locating every infected Indian within the state, with the view of securing proper care of and attention to individual cases and of preventing the further spread of the disease. (4) A careful examination should be made of every child enrolled in the public schools contiguous to the Indian reservation and in those at the different mining locations in the state, and the name and address of every infected child should be recorded and certified to the State Board of Health for such action as may be necessary for the ultimate elimination of this disease from the school population and the homes of these districts. (5) A complete examination of the eyes of every inmate confined in or attending a state institution should be made to detect cases of trachoma for the purpose of ensuring prompt and adequate treatment. (6) A mobile trachoma unit should be organized at state expense and authorized to travel to infected points for the purpose of giving necessary treatment and familiarizing the local physicians with the most recent and effective methods of cure. (7) Arrangements should be perfected whereby certain hospitals located at strategic points from the standpoint of trachoma prevalence, may be utilized, at state expense when necessary, for the hospitalization of infected cases requiring hospital treatment occurring in the white population. (8) In order more effectively to eliminate trachoma in the district formerly comprising the White Earth Indian Reservation, a hospital should be operated by the state

at some readily accessible point in this district for the proper management of all trachoma cases found among the former wards of the Government. (9) A coöperative arrangement should be entered into with the United States Office of Indian Affairs for the purpose of enforcing measures necessary for the control of trachoma among that portion of the Indian population of the state remaining under Government guardianship; otherwise, owing to improved facilities for intercommunication, the elimination from the non-reservation population will be greatly complicated, if not impossible.

A Preliminary Report on the Use of Creosote Oil as a Mosquito Repellent.—Coogle (*Pub. Health Rep.*, 1923, **38**, 443) gives the following as a summary of his observations: "These observations indicate that creosote oil, when applied to the walls and ceilings of certain houses, in the quantity of 1 gallon to 420 square feet, will noticeably repel anopheline mosquitoes. The duration of its effectiveness is yet to be determined. Observations made of certain of the creosoted houses ten weeks after the creosote had been applied seem to indicate that the creosote oil was still effective. It appears the creosote oil as a mosquito repellent is particularly applicable to and desirable for use in houses of poor construction, where screening and other antimosquito measures cannot be effectively employed. Apparently colored people who commonly live in houses of this type in the southern states do not object to the application of creosote oil in the quantities employed in these observations. Unquestionably it is less objectionable than the smudges of rags, leather and feathers, so universally used by these people to keep the mosquitoes away while they secure a few hours' sleep. Apparently, the employment of creosote oil in the quantity and manner indicated above is perfectly safe. No ill-effects were noted upon any of those who slept in the rooms subsequent to the application of creosote oil. One observation seems to indicate that creosote may be used to prevent mosquitoes from laying eggs in water barrels."

Dried Milk Powder in Infant Feeding.—Clark and Collins (*Pub. Health Rep.*, 1922, **37**, 2415) found the milk prepared from dried milk powder was quite satisfactory for infant feeding. Neither scurvy nor rickets seemed to follow the use of the preparation and the general results from the point of view of nutrition were good. This work confirms the impression gained earlier on less adequate data.

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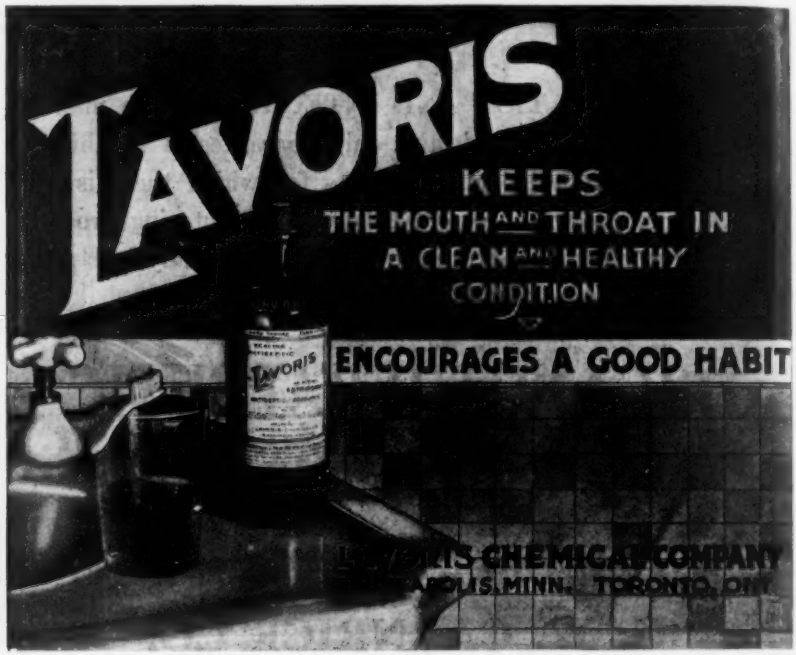

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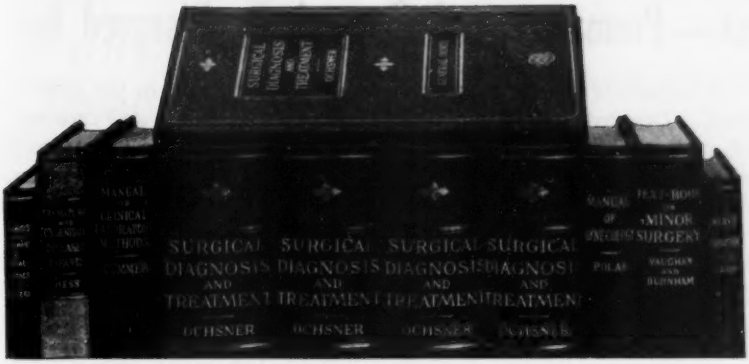

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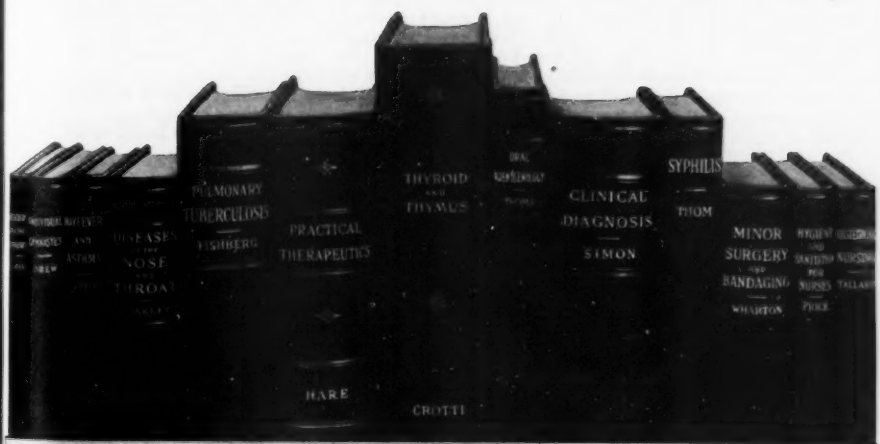

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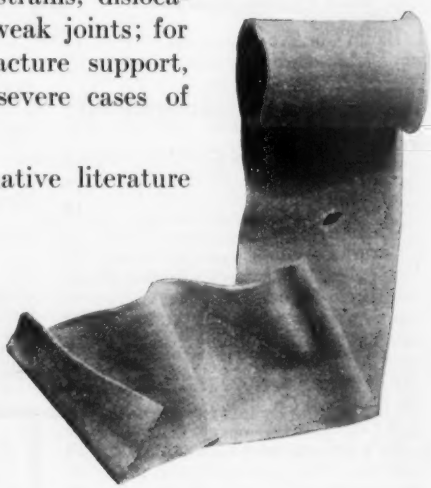

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INDEX

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